

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY and MANULIFE
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF JAMES THOMAS

I, James Thomas, hereby declare and say:

1. My name is James Thomas. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

Education and Professional Background

2. I am currently employed by Abbott Laboratories (“Abbott”) as a manager in Statistics. I became employed by Abbott in 1995.

3. I received a B.S. in Statistics and an M.S. in Statistics from Brigham Young University in 1989 and 1991, respectively.

4. Prior to joining Abbott in 1995, I worked as a statistician at Parexel International, a contract research organization (“CRO”), for approximately three and a half years. In 1995, I joined Abbott as an Associate Statistician. I remained in that position until 2000 or 2001, when I was promoted to Senior Statistician I. In approximately 2003, I was promoted to Senior Statistician II, a position I occupied until I was appointed in 2005 to my current position as Manager of Statistics.

5. During my employment as an Abbott Senior Statistician I and II, and as Manager of Statistics, I have been responsible for helping to design clinical trials of compounds in Phase II and Phase III of development, for reviewing clinical trial protocols, case report forms, and clinical study reports. As Senior Statistician II and Manager of Statistics, I have also been responsible for supervising other Abbott statisticians.

6. Throughout my employment at Abbott, I have also been responsible from time to time for helping to prepare reports for Abbott’s management regarding the status of Abbott’s clinical trials and regarding the clinical trials of compounds that have been or are being developed by Abbott’s competitors in the pharmaceutical industry. Abbott regularly obtains detailed information about the clinical trials of competitors’ compounds from publicly available sources, including articles in scientific journals. In order to fulfill my responsibilities at Abbott, it is necessary for me to remain current on developments in statistical issues in clinical trials at Abbott and at competitors, and I do so by participating in meetings and presentations at Abbott at which such developments are presented and discussed and by reading Abbott clinical study reports and journal articles and other publicly available sources of information.

7. During my employment as a statistician at Abbott, I have worked on approximately 25 Phase II and Phase III clinical trials for compounds in development by Abbott.

ABT-594

8. ABT-594 is an analgesic compound that was under development in the Analgesia Venture at Abbott from 1997 through October 2001. I worked as a statistician on ABT-594 during this period. ABT-594 is a member of a class of compounds known as cholergeric channel modulators (“CCM”) or neuronnic nicotinic receptors (“NNR”). My responsibilities with regard to ABT-594 included consulting with the clinical team in the design of Phase II clinical trials and in the development of the protocols for each of the Phase II clinical trials, preparing sections of each of the protocols (especially those sections dealing with statistical matters), developing and supervising the analyses for the final clinical study report, and writing sections of the clinical study report.

9. I participated in the preparation of the Protocol and the final Clinical Study Report for the ABT-594 M99-114 Phase IIb clinical trial. Attached hereto as Exhibits 603 and 795, respectively, are true and correct copies of the Protocol and the Clinical Study Report.

10. My work on each of the ABT-594 clinical trials included the calculation of the planned power of the trials. I did not choose what the planned power of the trials should be. That was a decision made by the ABT-594 clinical team.

11. The original planned power of the M99-114 trial was 80%. However, in my experience at Abbott it was not unusual for clinical trials such as the ABT-594 Phase II clinical trials to be designed at different levels of planned power. In my experience,

Abbott sometimes sets planned power of its Phase II trials at 80%, but at other times Abbott sets planned power at less than 80%. For example, in three ABT-594 Phase II studies other than the M99-114 trial discussed above, Abbott designed each trial to have less than 80% planned power. For a Phase II Osteoarthritis Pain trial, M98-826, which was a 256 patient, randomized, double-blind, placebo-controlled trial, the planned power of the trial was 56%. The planned power of the Neuropathic Pain trial, M98-833, a 133 patient, randomized, double-blind, placebo-controlled, multiple dose trial, was also 56%. For the Molar Extraction study, M97-772, a 290 patient, randomized, double-blind, placebo-controlled, single dose trial, the planned power was 70%. Attached hereto as Exhibits MI, MJ, and MK are true and correct copies of the clinical protocols of each of these three trials.

12. I am also aware that Abbott has planned the power of Phase III clinical trials at less than 70%. For example, I worked approximately ten years ago on the design and protocol of a Phase III trial for the compound now known as Depakote, an Abbott drug for the treatment of several indications, including bipolar disorder and epilepsy. For this Phase III trial, the Abbott Depakote clinical team selected a power of 70%.

13. In 2000, after Abbott had begun enrolling patients in the M99-114 clinical trial, I was asked to calculate, in a fully blinded manner, the effect of smaller sample sizes on the probability of detecting the M99-114's predefined standardized treatment effect of 0.46. My calculations in this regard assumed that all patients would be evaluable for efficacy. Attached hereto as Exhibit 573 is an email dated September 28, 2000, from me to Ms. Rebecca L. Brown containing an example of such power calculations. I was also asked to consider the effect on the power of the study of smaller sample sizes on the

probability of detecting standardized treatment effects smaller and larger than 0.46.

Attached hereto as Exhibit 566 is a true and correct copy of an email dated August 29, 2000, from me to Ms. Catherine K. Kacos, containing an example of such calculations.

Early Terminations of Patients From Trials of Pain Compounds

14. Before the M99-114 study was unblinded, I did not regard the early termination rate or the proportion of early terminations for adverse events to be necessarily a problem for the potential success of the study or the compound. In studies for some types of compounds, an early termination rate of close to 50% of patients enrolled in a clinical pain trial, as was experienced in the ABT-594 M99-114 trial, is not inappropriate or unexpected. Specifically, based on my experience at Abbott and my review of publicly available information, I was aware in 2000 and 2001 that early termination rates for clinical trials of some types of pain compounds in particular can be in the range of 40 to 60%, and sometimes higher. I was also aware that many compounds for the treatment of chronic pain, including many opioids, have experienced high rates of early terminations in clinical trials, yet are widely considered to be effective for a variety of different types of chronic pain and have been approved by the FDA. Based on my experience, these facts are well-known at Abbott and in the pharmaceutical industry generally.

15. In late 2000 and in 2001, I was aware from my work at Abbott that clinical trials of tramadol, controlled release codeine, and controlled release oxycodone, among other pain compounds, had shown that the compounds were efficacious despite experiencing dropout rates ranging from one-third to more than half of the total number of patients enrolled in the trial. For example, an article in the *Archives of Internal Medicine* reported in 2000 that 52.6% of the patients enrolled in a double-blinded, placebo-controlled trial

of controlled release oxycodone discontinued their participation in the study, and that 40% of those early terminations were due to adverse events. A true and correct copy of this article from the *Archives of Internal Medicine* is attached hereto as Exhibit ML. Despite these early termination rates, tramadol, controlled release codeine and controlled release oxycodone have all been approved for marketing by the FDA.

16. Based on my work at Abbott, I am aware that since 2001 other pain compounds have been approved by the FDA for marketing despite experiencing high dropout rates in Phase II and/or Phase III clinical trials, and that Abbott relies upon this fact in its development of its own pain compounds. For example, I am aware that we have discussed at Abbott that in a Phase III clinical trial for AVINZA™, a pain drug that was approved in March 2002 by the FDA for the relief of moderate-to-severe pain, the blinded early termination rate was approximately 42% (87/205) and that approximately 26% of the patients at the highest dose dropped out due to adverse events.

17. I am currently working as a statistician on a pain compound in development at Abbott known as Vicodin Controlled Release (“Vicodin CR”). Vicodin CR is an opioid. Abbott recently completed a Phase II double-blinded, placebo-controlled clinical trial (M03-643) for Vicodin CR. I participated in the design of this study, in the preparation of the protocol, and in the analysis of the data from the study.

18. Based on my analysis in the ordinary course of my work for Abbott of the data from Abbott’s M03-643 Vicodin CR study, I am aware that approximately 40% of the total number of randomized patients who participated in the trial (including active dose and placebo) failed to complete that trial (47% and 32%, respectively). I am also aware that 31% of the total number of randomized patients in the active treatment group

terminated early because of adverse events. Put another way, nearly 70% of the early terminations in the active treatment group were attributable to adverse events.

19. Based in part on the results of the M03-643 Vicodin CR Phase II study, which reached a statistically significant endpoint, Abbott decided to move forward into Phase III in the development of the compound.

20. More recently, Abbott completed a Phase III double-blinded, placebo-controlled clinical trial (M04-697) for Vicodin CR. I participated in the design of this pivotal Phase III study, in the preparation of the protocol, and in the analysis of the data from the study.

21. Based on my analysis in the ordinary course of my work for Abbott of the data from Abbott's M04-697 Vicodin CR Phase III study, which reached many statistically significant endpoints, I am aware that 45% of the patients who received Vicodin CR and 43% of the placebo patients dropped out of the study early. Of the 192 patients who received Vicodin CR in this study who dropped out early, more than half (100 patients) dropped out early because of adverse events.

22. I participated in the preparation and filing of the New Drug Application ("NDA") that Abbott recently submitted to the FDA for approval of Vicodin CR. Abbott's Vicodin CR NDA is based in part on the results of the M04-697 Phase III trial described above.

I declare under penalty of perjury, under the laws of the United States of America, that the foregoing is true and correct. Executed this 9th day of March 2008, at Grayslake, Illinois.



JAMES THOMAS



James W
Thomas /LAKE/PPRD/ABBO
TT

08/29/2000 03:31 PM

To Catherine K Kacos/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject Re: M99-114 graph data

----- Forwarded by James W Thomas/LAKE/PPRD/ABBOTT on 08/29/2000 03:31 PM

David G Jaskela
08/29/2000 02:56 PM

To: James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Re: M99-114 graph data



ABT-594.ppt

JAMES W THOMAS

JAMES W THOMAS

08/29/2000 02:19 PM

To: David G Jaskela/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: M99-114 graph data

Attached and below is the data for the 2 graphs.....

OBS	SAMPLE SIZE	EFFECT	POWER	CON
1	20	0.45	0.28380	0.63263
2	25	0.45	0.34451	0.71836
3	30	0.45	0.40297	0.78719
4	35	0.45	0.45862	0.84132
5	40	0.45	0.51108	0.88313
6	45	0.45	0.56013	0.91489
7	50	0.45	0.60564	0.93867
8	55	0.45	0.64760	0.95624
9	60	0.45	0.68606	0.96906
10	65	0.45	0.72111	0.97831
11	70	0.45	0.75292	0.98492
12	75	0.45	0.78165	0.98959
13	80	0.45	0.80751	0.99287
14	20	0.50	0.33794	0.70980
15	25	0.50	0.41010	0.79473
16	30	0.50	0.47790	0.85768
17	35	0.50	0.54069	0.90310
18	40	0.50	0.59815	0.93511
19	45	0.50	0.65019	0.95719
20	50	0.50	0.69689	0.97215
21	55	0.50	0.73849	0.98212
22	60	0.50	0.77527	0.98865
23	65	0.50	0.80758	0.99288
24	70	0.50	0.83582	0.99557
25	75	0.50	0.86037	0.99728

7

CONFIDENTIAL
ABBT0080232

26	80	0.50	0.88160	0.99834
27	20	0.55	0.39576	0.77939
28	25	0.55	0.47837	0.85807
29	30	0.55	0.55365	0.91108
30	35	0.55	0.62107	0.94559
31	40	0.55	0.68059	0.96741
32	45	0.55	0.73249	0.98086
33	50	0.55	0.77727	0.98895
34	55	0.55	0.81555	0.99372
35	60	0.55	0.84800	0.99649
36	65	0.55	0.87532	0.99806
37	70	0.55	0.89816	0.99894
38	75	0.55	0.91715	0.99943
39	80	0.55	0.93285	0.99970
40	20	0.60	0.45603	0.83904
41	25	0.60	0.54731	0.90723
42	30	0.60	0.62750	0.94832
43	35	0.60	0.69653	0.97205
44	40	0.60	0.75495	0.98529
45	45	0.60	0.80370	0.99244
46	50	0.60	0.84388	0.99619
47	55	0.60	0.87664	0.99812
48	60	0.60	0.90312	0.99909
49	65	0.60	0.92433	0.99957
50	70	0.60	0.94119	0.99980
51	75	0.60	0.95452	0.99991
52	80	0.60	0.96498	0.99996



smaller.lst

CONFIDENTIAL
ABBT0080233

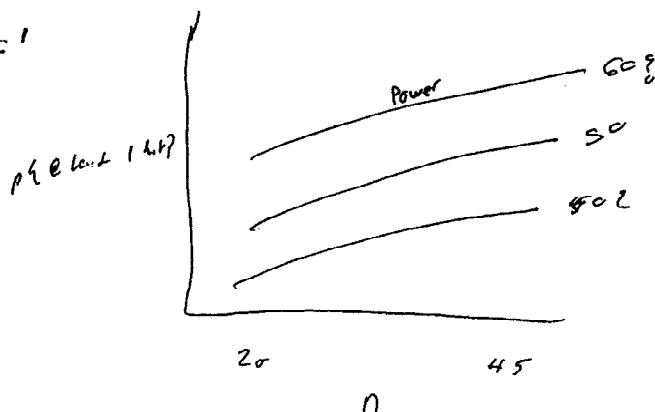
(3)

$$\frac{3!}{2!1!} = 3$$

(3) (6)

$$\begin{array}{l} (3) .5^3 \quad \text{---} \quad 3 \times .25 \times .5 \\ (3) \quad \text{---} \quad 3 \\ (3) \quad \text{---} \quad 1 \end{array}$$

$$\frac{.125}{7} = .017857$$



(62)

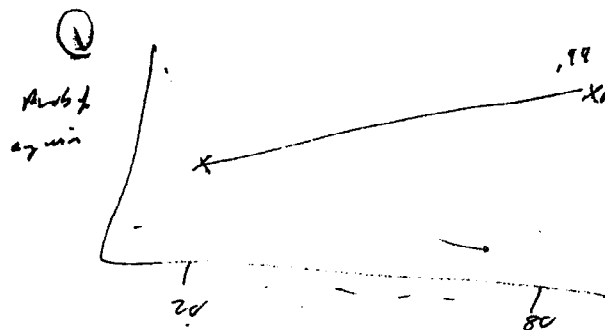
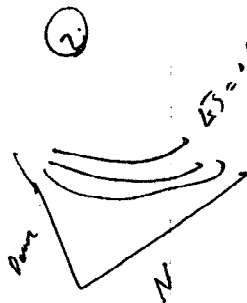
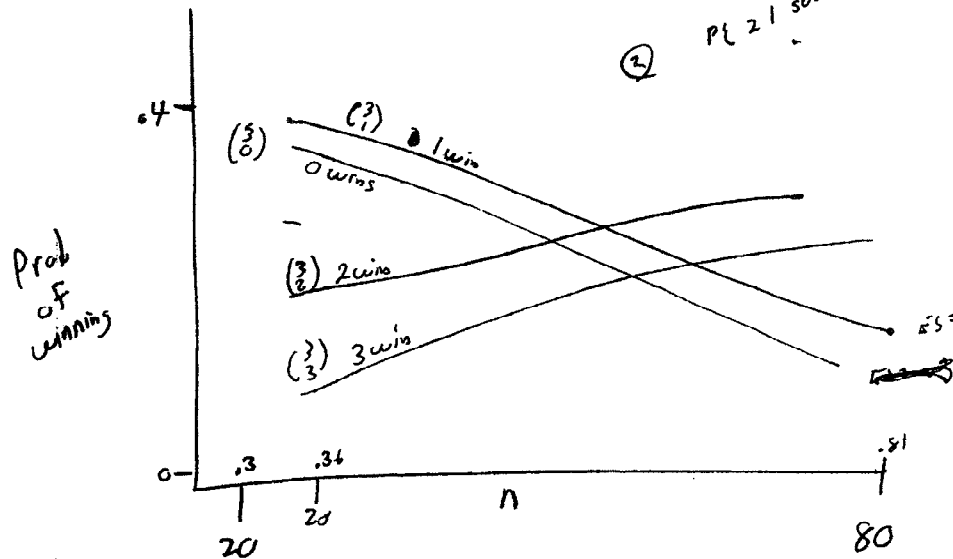
$$\begin{array}{r} 62 \\ \times 4 \\ \hline 248 \end{array}$$

$$\begin{array}{r} 54 \\ \times .6 \\ \hline 324 \end{array}$$

① Set ES
 $n = 20 \text{ to } 80$

Phum

② PL 21 success / $p = \text{pound}$



ES = 0.4
 0.30

$$\begin{aligned} & \binom{3}{0} p^0 (1-p)^3 \\ & {}^n \binom{3}{1} (p)^1 (1-p)^2 \\ & \binom{3}{2} (p)^2 (1-p)^1 \\ & \binom{3}{3} (p)^3 (1-p)^0 \end{aligned}$$

	Power	$\binom{3}{1}$ ↓	$\binom{3}{2}$ ↓	$\binom{3}{3}$ ↓	$\binom{3}{0}$
20	.3	.447 .441	.189	.027	.343
25	.36	.442	.249	.047	.262
30	.42	.424	.307	.074	.195
35	.48	.389	.359	.111	.141
40	.53	.351	.396	.149	.104
45	.58	.307	.424	.195	.074
50	.62	.269	.438	.238	.055
55	.67	.219	.444	.301	.036
60	.71	.179	.439	.358	.024
65	.74	.150	.427	.405	.018
70	.77	.122	.409	.457	.012
75	.79	.105	.393	.493	.009
80	.81	.088	.374	.531	.007

Prob of ≥ 1 win

n	Power	$\frac{.46}{.50}$
20	.3	.657
25	.36	.738
30	.42	.805
35	.48	.859
40	.53	.896
45	.58	.926
50	.62	.945
55	.67	.964
60	.71	.976
65	.74	.982
70	.77	.988
75	.79	.991
80	.81	.993

.50.46 effect

$$1 - [1.1 \cdot (1 - p)^3]$$

.253

$$1 - (1 - p)^3$$

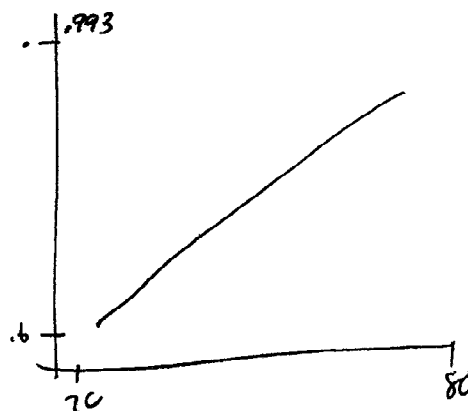
$$\binom{3}{0} = 1 \cdot p^0 \cdot (1-p)^3$$

Power	Cond Prob
.23380	.633
.34451	.718

.80751

Prob ≥ 1
win

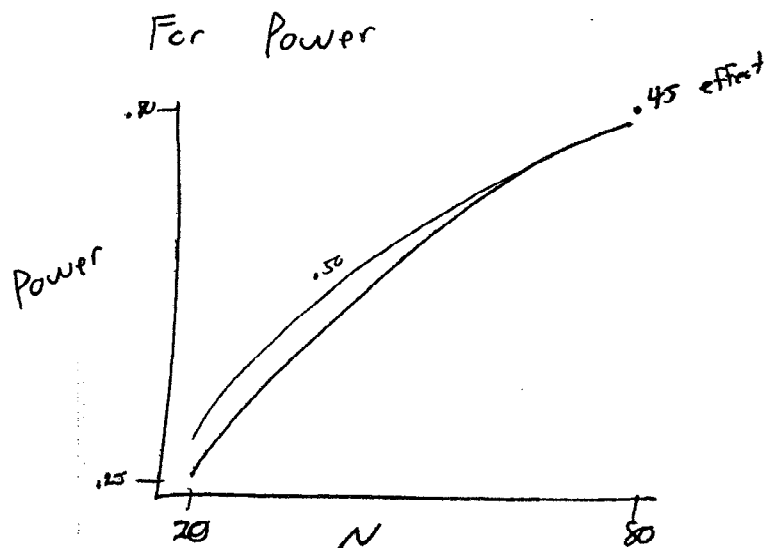
Fixed effect size



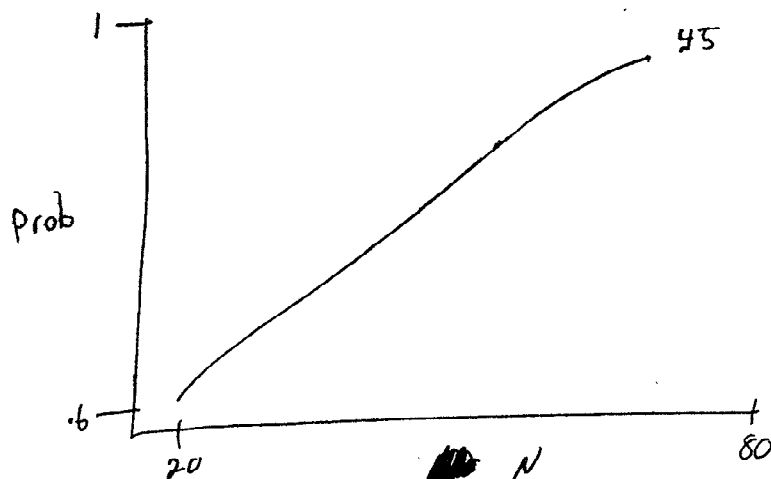
.46

<u>N</u>	<u>Power</u>	<u>cond Prob</u>
20	.3	.657
25	.36	.738
30	.42	.805
35	.48	.859
40	.53	.896
45	.58	.926
50	.62	.945
55	.67	.964
60	.71	.976
65	.74	.982
70	.77	.988
75	.79	.991
80	.81	.993

Thomasj/ABT-594/M99-114/Power/smaller.sas



For Conditional (Prob^{ability} of ≥ 1 treatment group beating placebo)



JAMES W THOMAS

09/27/2000 02:05 PM

To: David D Morris/LAKE/PPRD/ABBOTT @ ABBOTT

cc:

Subject: 114 slides for sample size

David, this is something that we prepared for the
114 study.....

Assumptions for the Likely Range of Differences for the True Effect Size for the Neuropathic Pain Study

Scenario 2 (there were 5 that we presented to the venture)

Results based the baseline and standard deviation data observed in the Abbott M98-833 study and then assuming a 39% change from baseline to final for the ABT-594 75 mcg group in M98-833 (a 39% change was seen for the primary analysis in the Gabapentin study). A 25% placebo response is assumed for this scenario.

Mean changes from baseline:

ABT-594 = 26.5

Placebo = 15.1

Treatment Difference = 11.4

MSE from ANOVA model for change from baseline to final = 24.4

Effect Size $(11.4/24.4) = 0.47$

Source: Abbott study M98-833, analysis of NPS total score for diabetics, change from baseline to final, 2-way ANOVA without interaction, locf (placebo = $60.4 \times .25 = 15.1$; ABT-594 = $67.9 \times .39 = 26.5$).

The M98-833 results show a 10% placebo response, which is not a likely placebo response for this pain model. Thus, an estimate of a 25% placebo response is used here.

For M98-833, 61 (46% -- 61 of 133) patients were diabetics

(24 pt in placebo, 19 in 25 mcg, and 18 in 75 mcg) .

114 protocol wording for sample size is.....

This calculation (n=80 per group for a .46 effect size) is based on results obtained from 833 and published data using Gabapentin for subjects with painful diabetic polyneuropathy and assuming a 39% and a 25% improvement from baseline for 594 and placebo, respectively.

M99-114

(A)

Sample Size Rationale

$N = 320$ (80% up)

Type I error: 0.05

Power: 80%

Effect size: 0.46

Sources

(+)

1. M99-833

N, R, sd

2. Gabapentin results in TAMA

N, R, sd

} data from Jiri

(B)

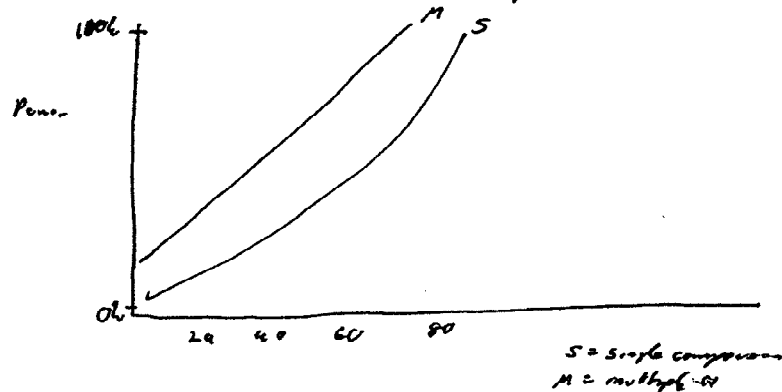
Show the standard power curve

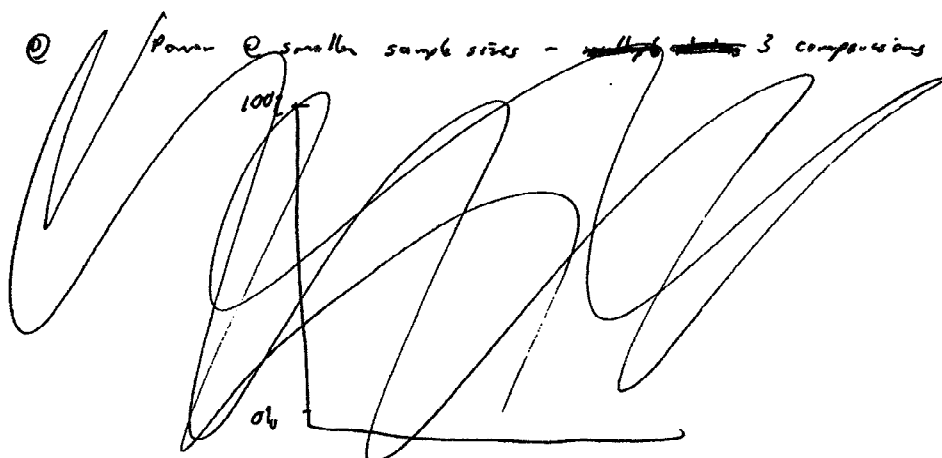
- gradual slope

near the asymptote

(C)

Power @ smaller sample sizes - ~~single comparison~~





③ Assumptions for calculating power of 3 comparisons

- Probability of single success is power of single comparison
- All doses are in efficacious range
- Comparisons are independent

~~Estimate Range of~~



Increases Type I error rate

④

Perspective of estimation

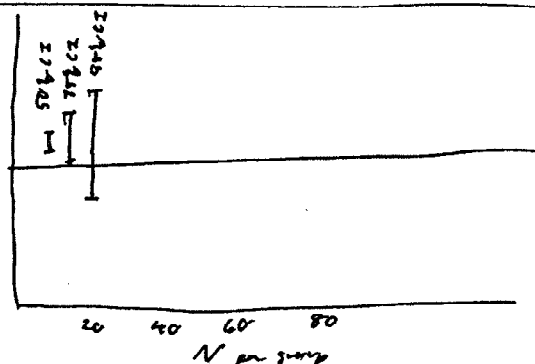
~~Observation to be~~

(Results available)

sample size

assumptions)

Prob
Diff



(A)

~~WUWUWU~~

Active Treatment

ABT-594 75mcg: ~~21%~~ ³⁸ for NPS Total

Gabapentin: 39% diary

(X)

Placebo

ABT-594 75mcg: 10%

Gabapentin: ~~21%~~ ^{23%}

ABT-594 n=18 diabetics only

PBO n=24 diabetics only

ABT-594 \bar{x} = mean Δ from ^{Placebo} ~~PBO~~ = ~~25.3~~ 25.3
 SD error = 7.3

Gaba ~~N=229~~ ~~completed = 184~~ ~~(80.3%)~~N=165 completed: ~~82%~~ ^{82%} (135)Gaba n=82 mean Δ = ~~3.9~~ 3.9

PBO n=80 " " = 5.1


PART 1

ABBOTT LABORATORIES
Clinical Protocol

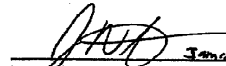
**A Randomized, Double Blind, Placebo-Controlled, Comparison
of the Safety and Efficacy of ABT-594 to Placebo in Subjects
with Painful Diabetic Polyneuropathy**

Protocol M99-114

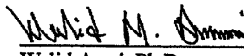
February 8, 2000


Fred Siebert, MT-BB (ASCP)
Senior Clinical Research Associate, Analgesia Venture

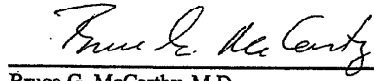
2/10/2000
Date

 *James Thomas for*
David Morris, Ph.D.
Manager, Clinical Statistics

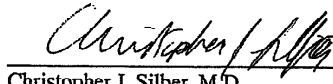
2-11-00
Date


Walid Awni, Ph.D.
Manager, Clinical Pharmacokinetics

2/11/00
Date


Bruce G. McCarthy, M.D.
Associate Medical Director, Analgesia Venture



2/10/00
Date


Christopher J. Silber, M.D.
Venture Head, Analgesia Venture

2/10/00
Date

 **Abbott Laboratories**

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

 DER EX. NO. 5
FOR ID., AS OF 4/13/07 

Confidential
ABBT0065818

ABT-594
Protocol M99-114
February 8, 2000

i

1.0 Title Page

Abbott Laboratories
Analgesia Venture, D48Q
Clinical Study

**A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety
and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic
Polyneuropathy**

ABT-594/M99-114
February 8, 2000

Development Phase: II

Investigators: Multicenter Trial

Estimated Date of First Subject to be Dosed: April 2000

Estimated Date of Last Subject to Complete Dosing: November 2000

Sponsor/Emergency Contact: Christopher J. Silber, M.D.
Venture Head,
Analgesia Venture
Phone: (847) 938-5236, Fax: (847) 938-5258
Department 48Q, Building AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193

This study will be conducted in compliance with Good Clinical Practice, including
the archiving of essential documents.

Confidential Information

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065819

ABT-594
Protocol M99-114
February 8, 2000

ii

2.0 Study Synopsis

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Hard Gelatin Capsule (HGC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Part of the Dossier: Not Applicable (N/A) Volume: N/A Page: N/A	<i>(For National Authority Use Only)</i>
Title of Study: A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter Study		
Study Center(s): 30		
Publication (reference): N/A		
Study Period (years): Estimated Date of First Subject to be Dosed: April, 2000 Estimated Date of Last Subject to Complete Dosing: November, 2000		Phase of Development: II
Objectives: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.		
Methodology: This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg, or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll 320 subjects who meet entry criteria for this study. Prior to any study-specific procedures at the Screening Visit, an informed consent will be signed and study eligibility determined.		

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065820

ABT-594
Protocol M99-114
February 8, 2000

iii

Methodology: (Continued)

Prior to study drug administration, subjects will have discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and have completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who meet entry criteria, will be randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Treatment Phase, subjects will return to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). During the Primer and Treatment Phases, subjects will be allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but will not be allowed to take acetaminophen within 24 hours prior to a Treatment Visit). Subjects will complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects will undergo site-based assessments of their neuropathy pain at the Baseline Visit and Treatment Visits I, II, III and IV. Subjects will discontinue study drug administration after Treatment Visit IV and return to the site for the Follow-Up visit 7-10 days later. See Figure 9.1a, Study Schematic, for additional study layout information.

Efficacy and safety assessments will include: the Pain Rating Scale (11-Point Likert), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change.

No. of Subjects: 320

Diagnosis and Main Criteria for Inclusion:

A subject may be randomized in this study provided that he/she meets all of the Inclusion Criteria outlined below and does not meet any of the Exclusion Criteria in Section 9.3.2.

- Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.
- The subject must be age 18 or older and in relatively good health with a recent stable medical history.
- The subject's weight must be \leq 265 pounds.
- A female subject must be non-lactating and:
 - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),
 - OR
 - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative β subunit human chorionic gonadotropin (β -hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β -hCG at all Treatment Visits.

- The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065821

ABT-594
Protocol M99-114
February 8, 2000

iv

- The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- The subject must have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) everyday during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

Test Product(s): ABT-594 75 μ g HGC (Formulation A-2)

Dose: ABT-594 150 μ g, 225 μ g, or 300 μ g BID (Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
ABT-594 75 μ g HGC	58-293-AR

Duration of Treatment: 49 days

Reference Therapy: Placebo for ABT-594 HGC No. 1 Light Gray Opaque (Starch)

Dose: Placebo to match test product (see Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
Placebo for ABT-594 HGC	55-243-AR-01

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065822

ABT-594
Protocol M99-114
February 8, 2000

vi

Statistical Methods: (Continued)

Mean change from baseline to minimum, maximum and final values will be summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits will be flagged in the data listings. Furthermore, laboratory results which satisfy the criteria for limits for statistical analysis will be identified.

To assess dose proportionally and time invariance (from Visit I to Visit IV), dose-normalized C_{trough} and log-transformed dose-normalized AUC, and C_{max} from the subset of subject participating in intensive pharmacokinetic sampling will be subjected to a mixed effects model analysis with effects for dose level, visit, relevant covariates, and perhaps study center. The logarithmic transformation will be employed for AUC and C_{max} . An exploratory analysis will also be performed on the data set obtained from all subjects.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065824

ABT-594
Protocol M99-114
February 8, 2000

vii

3.0 Table of Contents

	Page
1.0 Title Page	i
2.0 Study Synopsis	ii
3.0 Table of Contents	vii
4.0 List of Abbreviations and Definitions of Terms	xi
5.0 Ethics	1
5.1 Institutional Review Board or Independent Ethics Committee ..	1
5.2 Ethical Conduct of the Study	1
5.3 Subject Information and Consent	1
5.4 Subject Confidentiality	2
6.0 Investigators and Study Administrative Structure	3
6.1 Investigative Sites	3
6.2 Sponsor Information	3
6.3 Contract Research Organization	3
6.4 Clinical Supply Management	3
6.5 Central Laboratory	4
6.6 Administrative Structure	5
7.0 Introduction	6
7.1 Analgesia Today	6
7.2 ABT-594	6
8.0 Study Objectives	9
9.0 Investigational Plan	10
9.1 Overall Study Design and Plan: Description	10
9.2 Discussion of Study Design, Including the Choice of Control Groups	14
9.3 Selection of Study Population	14

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065825

ABT-594
Protocol M99-114
February 8, 2000

viii

Table of Contents (Continued)

	Page
9.3.1 Inclusion Criteria	14
9.3.2 Exclusion Criteria	15
9.3.3 Removal of Subjects from Therapy	16
9.4 Treatments	17
9.4.1 Treatments Administered	17
9.4.2 Identity of Investigational Products	19
9.4.2.1 Packaging and Labeling	19
9.4.2.2 Storage and Disposition of Supplies	19
9.4.2.3 Drug Accountability	20
9.4.3 Method of Assigning Subjects to Treatment Groups	20
9.4.4 Selection of Doses in the Study	21
9.4.5 Selection and Timing of Dose for Each Subject	21
9.4.6 Blinding	21
9.4.7 Prior and Concomitant Therapy	21
9.4.8 Treatment Compliance	22
9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures	23
9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts	23
9.5.1.1 Efficacy Measurements	25
9.5.1.2 Safety Measurements and Procedures	26
9.5.2 Appropriateness of Measurements	34
9.5.3 Efficacy Variables	34
9.5.3.1 Primary Variable(s)	35
9.5.3.2 Secondary Variable(s)	35
9.5.4 Drug Concentration Measurements	35

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065826

ABT-594
Protocol M99-114
February 8, 2000

ix

Table of Contents (Continued)

	Page
9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay	35
9.5.4.2 Additional Pharmacokinetic Sampling	36
9.5.4.3 Shipment of Plasma Samples	37
9.5.5 Blood Samples for Genetic Polymorphism Analysis	37
9.6 Data Quality Assurance	38
9.7 Statistical Methods and Determination of Sample Size	39
9.7.1 Statistical and Analytical Plans	39
9.7.1.1 Data Sets Analyzed	40
9.7.1.2 Demographic and Other Baseline Characteristics	40
9.7.1.3 Efficacy Analyses	40
9.7.1.4 Safety Analyses	43
9.7.2 Determination of Sample Size	44
9.7.3 Pharmacokinetics/Pharmacodynamics	44
9.8 Changes in the Conduct of the Study or Planned Analyses	45
9.8.1 Protocol Changes	45
10.0 Protocol Deviations	46
11.0 Use of Information and Publication	46
12.0 Completion of The Study	47
13.0 Investigator's Agreement	48
14.0 References	49

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065827

PART 2

ABT-594
Protocol M99-114
February 8, 2000

x

Table of Contents (Continued)

	Page
List of Tables	
Table 9.4.1a ABT-594 Dose Escalation	18
Table 9.4.1b Number and Type of Capsules by Treatment Regimen	18
Table 9.4.2a Identity of Investigational Products	19
Table 9.5a Study Procedures Flow Chart	24
Table 9.5b Clinical Laboratory Tests	28
Table 9.5c Definitions for Investigator Rating of Adverse Event Severity	30
Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug	31

List of Figures

Figure 6.6a Administrative Structure	5
Figure 9.1a Study Schematic	13

List of Appendices

Appendix A Documents Required Prior to Initiation of the Study	50
Appendix B Declaration of Helsinki	51
Appendix C Responsibilities of the Clinical Investigator	55
Appendix D Elements of the Consent Form	56
Appendix E Sample Abbott Laboratories Drug Accountability Form Study M99-114	59
Appendix F Pain Assessments	60
Appendix G Neuropathic Pain Scale	61
Appendix H Subject Global Impression of Change and Clinician Global Impression of Change	63
Appendix I Laboratory Determinations, Vital Signs and Electrocardiogram Variables for Statistical Analysis	64

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065828

ABT-594
Protocol M99-114
February 8, 2000

xi

4.0 List of Abbreviations and Definitions of Terms

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or A-165594
CSI	Clinical Supplies Invoice
HGC	Hard Gelatin Capsules
IVRS	Interactive Voice Response System
nAChRs	Neuronal nicotinic acetylcholine receptors
NPRO	New Product Research Order
NPS	Neuropathic Pain Scale

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065829

ABT-594
Protocol M99-114
February 8, 2000

1

5.0 Ethics

5.1 Institutional Review Board or Independent Ethics Committee

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator will obtain a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories will receive documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year. A complete list of documents required prior to initiation of the study is located in Appendix A.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version, Appendix B) and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix C.

5.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065830

ABT-594
Protocol M99-114
February 8, 2000

2

signed and dated by the subject and the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of an Informed Consent are specified in Appendix D.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study will identify each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the CRFs.

The site will collect information on the subject per International Council on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency should also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site according to the record retention guidelines outlined in Section 12.0.

Neither the subject, the subject's physician, nor the investigator will be informed of the subject's pharmacogenetic results, should they be obtained. If performed, results from individual subjects will be kept confidential and will not be given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples will be stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples will be kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065831

ABT-594
Protocol M99-114
February 8, 2000

3

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Investigative sites will be selected by Abbott Laboratories. Approximately 30 sites will be selected to enroll subjects for this study.

6.2 Sponsor Information

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form will be generated by Abbott Laboratories. The database for this study will be created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories will be responsible for the statistical analysis of the data.

6.3 Contract Research Organization

Abbott Laboratories will delegate prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to a Contract Research Organization (CRO) for the conduct of this clinical study. The sponsor and CRO will maintain contact in order to manage adequately the progress of the study. The CRO will coordinate and perform all site visits and will prepare trip reports, using the Abbott format, for each visit performed. These reports will detail the activities conducted at all investigative sites and will include all relevant observations. All trip reports will be forwarded to the sponsor in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures (SOP).

6.4 Clinical Supply Management

Clinical supplies will be prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories will authorize the release of clinical supplies once the appropriate essential documents have been received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065832

ABT-594
Protocol M99-114
February 8, 2000

4

All subjects will be centrally randomized by site and assigned to a treatment group (using a randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS will be contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using a randomization supplied by Abbott Laboratories) will also be assigned using IVRS. Each site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records (Appendix E), and records for return of used and unused clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) will check drug accountability records regularly.

6.5 Central Laboratory

This study will utilize one central laboratory contracted by, and under the direction of, Abbott Laboratories. All protocol specified clinical laboratory tests will be performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

ABT-594
Protocol M99-114
February 8, 2000

5

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

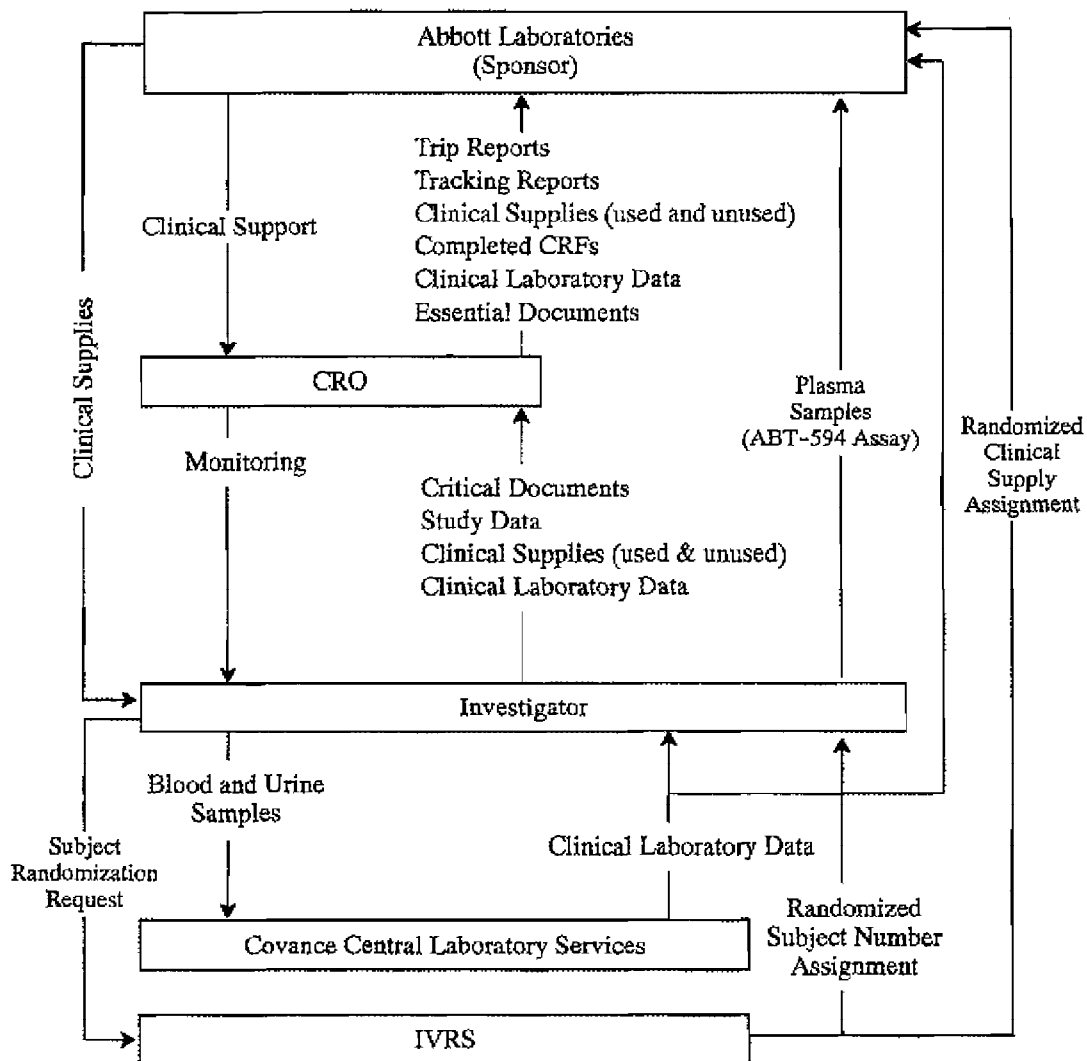


Figure 6.6a Administrative Structure

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065834

ABT-594
Protocol M99-114
February 8, 2000

6

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹

Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (+)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.² The antinociceptive effects of (+)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (+)-epibatidine appears to be a potent antinociceptive agent that

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065835

ABT-594
Protocol M99-114
February 8, 2000

7

acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (\pm)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.³ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

ABT-594
Protocol M99-114
February 8, 2000

8

Human clinical trials with ABT-594 began in 1997. Initial clinical trials were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 µg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Two Phase I studies with the HGC formulation have recently been completed: Study M99-076 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Ascending Doses of Twice Daily Dosing Regimens of a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects") and M99-120 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability and Pharmacokinetics of Escalating Doses of Twice Daily Dosing of a Hard Gelatin Capsule Formulation of ABT-594 in Adult Subjects in General Good Health"). Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120 included titrated doses up through 450 µg BID for 5 days. Adverse events, significantly different than placebo, for subjects receiving 300 µg BID for 14 days in Study M99-076 included: dizziness, nausea, vomiting, asthenia and diarrhea (all of which were considered to be mild in the opinion of the investigator). In addition, results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

Phase II has included (to date) efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon a study of molar extraction pain (Study M97-772, "A Randomized, Double-Blind, Single Dose Comparison of an Oral Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental Pain Model"), 100 µg ABT-594 (single dose oral solution) appeared to be a minimally efficacious dose in acute pain.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065837

PART 3

ABT-594
Protocol M99-114
February 8, 2000

9

A study of ABT-594 in osteoarthritis (Study M98-826, "A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain Associated with Osteoarthritis of the Knee") evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks and a study of ABT-594 in neuropathic pain (Study M98-833, "A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Patients with Painful Polyneuropathies") evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (greater than or equal to 5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature terminations).

Data from Phase I and II studies completed to date suggest that ABT-594 will be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, will be performed to test this hypothesis.

8.0 Study Objectives

The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065838

ABT-594
Protocol M99-114
February 8, 2000

10

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll approximately 320 subjects who meet entry criteria for this study.

The study will be divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 is the first day of study drug administration. Subjects will be allowed a window of ± 3 days for each study visit. The study design is depicted in Figure 9.1a.

Subjects will review and sign the informed consent prior to the conduct of any study specific procedures. Subjects will then be screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclics, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs (AEDs), or other analgesics for the treatment of their pain must have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase (Day -7 to Day -1). During the Baseline Pain Assessment Phase, subjects will complete, at approximately 11 AM each morning, the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity. Subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7) during the Baseline Pain Assessment Phase.

On the day after the Baseline Pain Assessment Phase, subjects will return to the site for their Baseline Visit (Day 1). At this visit, diaries will be collected and reviewed. In addition, subjects will complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who meet all entry criteria, including an average of ≥ 4 points on the

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065839

ABT-594
Protocol M99-114
February 8, 2000

11

diary-based Pain Rating Scale (11-Point Likert) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, will then complete the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects will undergo an interim medical history, physical examination, vital sign measurements, ECG and clinical laboratory tests.

Subjects who meet all entry criteria at the Baseline Visit will be randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID, or placebo. Subjects will start study drug at the evening dose on Day 1 (as specified in Section 9.4.5). During the Primer Phase, subjects randomized to ABT-594 will receive a fixed dose escalation of ABT-594 (as specified in Section 9.4.1). Following the Primer Phase, subjects will enter the Treatment Phase (Day 8) and will continue their treatment for a total of 49 days. During the Primer and Treatment Phases, subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7)

Subjects will complete the diary-based Pain Rating Scale each morning (approximately 11 AM), 3 hours after taking their morning dose of study drug. They will return to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV will include collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III) and efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute) (Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements and clinical laboratory tests (Treatment Visits I, III and IV), ABT-594 plasma assay collection (Treatment Visits I and IV only) and ECG (Treatment Visit IV only). A subset of subjects at selected sites will undergo intensive pharmacokinetic sampling at Treatment Visits I and IV.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065840

ABT-594
Protocol M99-114
February 8, 2000

12

On the day after Treatment Visit IV, subjects will enter the Post-Treatment Phase. Subjects will no longer take study drug or complete pain scales. Subjects may restart all discontinued medications under the guidance of their physician. Subjects will return for study procedures at the Follow-up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-up Visit will include physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participate in clinical studies of ABT-594 and who consent, a blood sample will be collected at Treatment Visit I in order to obtain a sample of genetic material (DNA). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

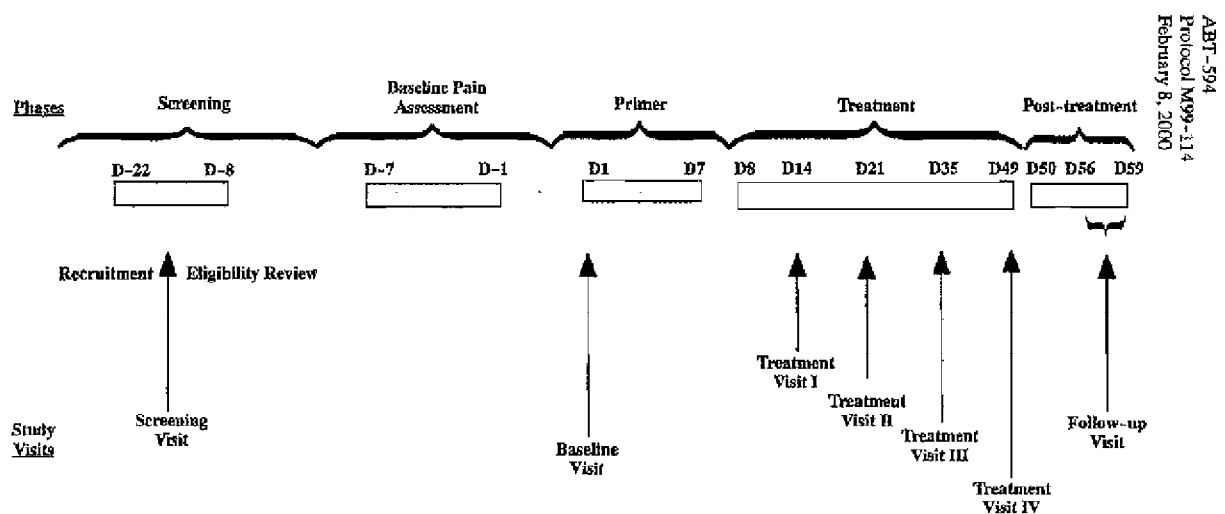


Figure 9.1a Study Schematic

13

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065842

ABT-594
Protocol M99-114
February 8, 2000

14

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provides a placebo control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales will be employed.

9.3 Selection of Study Population

It is anticipated that approximately 320 subjects will be randomized and receive study medication in this study. A subject may be randomized in this study provided that he/she meets all of the inclusion criteria outlined in Section 9.3.1 and does not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

9.3.1.1 Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.

9.3.1.2 The subject must be age 18 or older and in relatively good health with a recent stable medical history.

9.3.1.3 The subject's weight must be ≤ 265 pounds.

9.3.1.4 A female subject must be non-lactating and:

- of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),

OR

- of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative β subunit human chorionic gonadotropin (β -hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β -hCG at all Treatment Visits.

ABT-594
Protocol M99-114
February 8, 2000

15

- 9.3.1.5 The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- 9.3.1.6 The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam **and** either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.
- 9.3.1.7 The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- 9.3.1.8 The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- 9.3.1.9 The subject must have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

- 9.3.2.1 The subject has positive test results for drugs of abuse or viral hepatitis at the Screening Visit, or has a known history of a positive test result for HIV.
- 9.3.2.2 The subject has recent (< 5 years) history of drug or alcohol abuse or dependence.
- 9.3.2.3 The subject has an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.
- 9.3.2.4 The subject has active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that has been treated or other malignancies that have been surgically removed and have had no evidence of recurrence for a minimum of 5 years prior to study start).
- 9.3.2.5 The subject has taken an investigational drug within 1 month prior to administration of study treatment or is scheduled to receive an investigational drug other than ABT-594 during the course of this study.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065844

ABT-594
Protocol M99-114
February 8, 2000

16

- 9.3.2.6 The subject has a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.
- 9.3.2.7 The subject has orthostatic hypotension at the Screening Visit (as defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing), or a history of syncope or pre-syncope symptoms.
- 9.3.2.8 The subject has previously participated in a study involving ABT-594, including the present study.
- 9.3.2.9 The subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including AST or ALT \geq 1.5 times the upper limit of the reference range or a serum creatinine $>$ 1.5 mg/dL. Subjects may have elevated serum and urine glucose, but their serum glucose must have been under good control (in the opinion of the investigator) for at least the last 3 months prior to the Screening visit.
- 9.3.2.10 The subject has clinically significant electrocardiographic abnormalities.
- 9.3.2.11 The subject has ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.
- 9.3.2.12 The subject has a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject cannot differentiate from the neuropathy pain.
- 9.3.2.13 The subject has sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.
- 9.3.2.14 The subject is unlikely to comply with the study protocol or is unsuitable for any other reason, in the opinion of the investigator.

9.3.3 Removal of Subjects from Therapy

A subject may voluntarily terminate participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to

ABT-594
Protocol M99-114
February 8, 2000

17

terminate prematurely a subject's participation. The investigator must notify the CRA within 24 hours and document the reason for premature termination on the appropriate CRF.

Subjects, whose participation is terminated prematurely after signing study consent but before study drug administration, will not require follow-up observations. Subjects, whose participation is terminated prematurely after study drug administration must undergo procedures normally performed at Treatment Visit IV (see Table 9.5a) within 7-10 days following termination from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represents a significant risk to subjects, the study will be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID
ABT-594 225 µg BID
ABT-594 300 µg BID
Placebo for ABT-594 BID

ABT-594 and matching placebo will be supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects will receive a fixed dose escalation of ABT-594. ABT-594 will be initiated at 75 µg BID. The dose will increase every 2 days in 75 µg BID increments until subject are taking their assigned treatment dose (150, 225 or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4.1a.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065846

ABT-594
Protocol M99-114
February 8, 2000

18

Table 9.4.1a ABT-594 Dose Escalation

Treatment Regimen	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

Subjects will start study drug at PM dose on Day 1 (Section 9.4.5).

The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4.1b.

Table 9.4.1b Number and Type of Capsules by Treatment Regimen

Treatment Regimen		Number of Capsules Per Dose (Days 8-49)	
		Daily Blister Card (BID doses)	
		75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594	150 µg	2	2
ABT-594	225 µg	3	1
ABT-594	300 µg	4	0
Placebo		0	4

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065847

PART 4

ABT-594
Protocol M99-114
February 8, 2000

19

9.4.2 Identity of Investigational Products

Table 9.4.2a Identity of Investigational Products

Test Preparation Drug Product	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR	52-015-KD-00	Abbott ¹
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	N/A	Abbott ¹

¹ Pilot Plant, North Chicago, Illinois

ABT-594 75 µg HGC and placebo HGC are identical in appearance, encapsulated in Light Gray Opaque capsule size No. 1 HGCs.

9.4.2.1 Packaging and Labeling

Study drug supplies will be blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards will be provided to each subject.

Daily study medication cards will be labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space will be provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies must be stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies must be stored at controlled room temperature (68-77°F, see USP).

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065848

ABT-594
Protocol M99-114
February 8, 2000

20

9.4.2.3 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. Study drug will be dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who meets the enrollment criteria. The investigator or designee will record the subject number, subject initials and date dispensed to the subject on the Drug Accountability Form (Appendix E). The amount of study drug remaining will be recorded at Visits I, II, III and IV for each subject on the site Drug Accountability Form. An accurate running inventory of study drug will be kept and will include the NPRO number, CSI number(s), the number of modules dispensed and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for and returned to Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with the instructions of the CRA, will also be included in the shipment. The investigator agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects will be centrally randomized by investigative site using an Interactive Voice Response System (IVRS). Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site.

Approximately 320 subjects will be randomized in an equal ratio to receive either ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID or placebo. Subjects will be assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065849

ABT-594
Protocol M99-114
February 8, 2000

21

9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects will start study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects will then take BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs should be taken with at least one cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject will remain blinded to the subject's treatment throughout the course of the study. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) **MUST** be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. Blind breaking information will be provided using IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site. The sponsor must then be notified within 48 hours of the blind being broken. The date, and reason for blind breakage must be recorded on the appropriate CRF.

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks will be taken.

ABT-594
Protocol M99-114
February 8, 2000

22

Concomitant analgesics (prescription or over-the-counter [OTC] except aspirin and acetaminophen as described below), including serotonin-specific reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, muscle relaxants, TENS and topical analgesics will not be allowed.

Aspirin, 325 mg daily maximum, is permitted if taken for primary prevention of thromboembolic events and the dose has been stable for ≥ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, is permitted. Subjects will not be allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline Visit and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication is necessary during the course of this study, the medication name, dosage information, frequency and dates of administration must be reported on the CRF. Concomitant analgesic medication use (frequency only) will be recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and Treatment Visits I, II, III and IV. The concomitant medication use record will include the number of separate occasions each subject has used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects will be instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance will be documented by the investigator or designee on the site Drug Accountability Form (Appendix E) and on the appropriate CRF.

Overdose information will be collected on the appropriate CRF.

ABT-594
Protocol M99-114
February 8, 2000

23

9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures

9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Study procedures will be performed as summarized in Table 9.5a., Study Procedures Flow Chart.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065852

ABT-594
Protocol M99-114
February 8, 2000

24

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7		Treatment Phase D8-D49				Post-Treatment Phase D50-D59		
	Screening Visit		Baseline Visit D1	D2-D7	D8- D49	Treatment Visit					
						D14 I	D21 II	D35 III	D49 IV ^a		
Informed Consent	X										
Medical History	X		X ^b								X
Physical Exam	X ^c		X								X
Vital Signs	X ^d		X ^e								X ^f
ECG			X								X ^f
Clinical Laboratory Tests ^g	X		X								
Viral Hepatitis Screen	X										
Urine Drug and Alcohol Screen	X										
Pregnancy Test			X			X ^h	X ^h	X ^h	X ^h		
Genetic Polymorphism Sample (If Applicable)			X			X				X	
ABT-594 Plasma Assay						X				X	
ABT-594 PK Profile ⁱ						X				X	
Diary Issued	X		X			X	X	X	X		
Diary Collected			X			X	X	X	X		
Diary-Based Pain Rating Scale ^j		X		X							
Site-Based Pain Rating Scale			X			X	X	X	X		
Neuropathic Pain Scale			X			X	X	X	X		
Subject/Clinician Global Impression of Change										X	
SF-36 ^m			X							X	
Randomize Patient			X								
Dispense Study Drug			X			X ^k	X	X	X		
Analgesic Use Monitoring			X			X	X	X	X		
Adverse Event Monitoring			X			X	X	X	X		X
Concomitant Medication Monitoring			X			X	X	X	X		X
Study Drug Accountability		X				X	X	X	X		X

^a Required of all females of child-bearing potential.
^b Study drug must be taken in front of study staff. Blood samples from selected subjects will be taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.
^c To be completed at approximately 11 a.m. each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dosing during the Primer and Treatment Phases.
^d Redispense D15-22 Study medication after checking drug accountability.

^e Or upon premature termination.
^f Includes history.
^g Includes height.
^h Includes orthostatic measurements at Screening Visit only.
ⁱ Includes oral temperature at Baseline Visit only.
^j Performed only if there are clinically significant abnormalities at the previous evaluation.
^k Chemistry, hematology and urinalysis.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065853

ABT-594
Protocol M99-114
February 8, 2000

25

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer will instruct the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) will be the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments include the diary-based and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale and the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements should be performed (when possible) 3-4 hours post dose.

Pain Rating Scale (11-Point Likert Scale)

Subjects will assess pain intensity daily by completing the Pain Rating Scale (Appendix F) in their diaries. These assessments will be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects will record the time they completed these assessments in their diaries.

Subjects will also assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments will be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature termination). The time of assessment will be recorded on the appropriate CRF.

Neuropathic Pain Scale

The Neuropathic Pain Scale (Appendix G) will be completed by subjects at the Baseline Visit and at Visits I, II, III, and IV (or upon premature termination).

ABT-594
Protocol M99-114
February 8, 2000

26

Subject Global Impression of Change

The Subject Global Impression of Change (Appendix H) of analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

Clinician Global Impression of Change

The Clinician Global Impression of Change (Appendix H) of a subject's analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) will be completed by each subject at the Baseline Visit and at Treatment IV (or upon premature termination).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

Medical History

A complete medical history will be obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening will be recorded. The medical history will be updated at the Baseline Visit.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065855

ABT-594
Protocol M99-114
February 8, 2000

27

Physical Examination

A physical examination, including weight, will be performed at the Screening Visit, Baseline Visit, Treatment Visit IV and at the Follow-up Visit. Height will be measured at the Baseline Visit only. The physical examination performed at the Baseline Visit will serve as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate will be measured at the Screening Visit, Baseline Visit, Visits I, III, and IV and at the Follow-up Visit. Orthostatic blood pressure and pulse rate will be measured at the Screening Visit only. Oral temperature will be taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit will serve as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) should be obtained after the subject has been sitting for at least 3 minutes. Orthostatic measurements should be obtained after 3 minutes in the supine position and then after 1 minute in the standing position. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Subjects should not wear tight sleeves. Ideally, the subject's blood pressure should be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws. Subjects should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

Electrocardiogram (ECG)

A resting 12-lead ECG will be obtained at the Baseline Visit and Treatment Visit IV. An ECG will be performed at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The ECG performed at the Baseline Visit will serve as the baseline ECG.

A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the CRA with the CRF.

ABT-594
Protocol M99-114
February 8, 2000

28

Clinical Laboratory Testing

Samples will be obtained for the laboratory tests listed in Table 9.5.b at the Screening Visit, Baseline Visit (Day 1), and Treatment Visits I, III, and IV. Laboratory tests will be obtained at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The laboratory test results obtained at the Baseline Visit will serve as the baseline results. Blood draws should be performed after pain assessments or vital sign determinations during a visit.

Table 9.5b Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total bilirubin	pH
White Blood Cell (WBC) count	Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)	Bilirubin
Neutrophils	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Hemoglobin A _{1c} (Baseline Visit Only)	Chloride	
Lymphocytes	Calcium	
Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)	Inorganic phosphorus	
Platelet count (estimate not acceptable)	Uric Acid	
Prothrombin Time (PT)	Bicarbonate	
Partial Thromboplastin Time (PTT)	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065857

PART 5

ABT-594
Protocol M99-114
February 8, 2000

29

The investigator will review all laboratory test results and will assess clinical significance for each abnormal result. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A copy of each laboratory report must be included with the CRF.

Viral Hepatitis Screen

Subjects will undergo serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody) at the Screening Visit. The hepatitis test panel will be performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens will be tested for drugs of abuse and alcohol at the Screening Visit and will be performed by the central laboratory.

Pregnancy Test

A urine pregnancy test will be performed by designated study personnel at the Baseline Visit for all female subjects and at Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female will not be eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected and unfavorable event such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of a drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject.

The subject will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken and all adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be reported on the appropriate CRF.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065858

ABT-594
Protocol M99-114
February 8, 2000

30

The investigator will assess and record any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known), severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

Table 9.5c Definitions for Investigator Rating of Adverse Event Severity

Rating	Definition
Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065859

ABT-594
Protocol M99-114
February 8, 2000

31

Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Rating	Definition
Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

Adverse events will be monitored continuously from the time of study drug administration to the Follow-up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature termination) will be collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects will be instructed to report to the investigator any other adverse events that occur after Follow-up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures that occur after signing the Informed Consent and prior to the first dose of study drug will also be collected.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065860

ABT-594
Protocol M99-114
February 8, 2000

32

Ongoing medical conditions will be considered adverse events if there is an increase in severity or frequency of occurrence. Since measurements of pain intensity are efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study will not be considered adverse events for the purposes of this study.

Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to Abbott Laboratories as a serious adverse event (SAE) within 24 hours of occurrence or notification to the site:

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065861

ABT-594
Protocol M99-114
February 8, 2000

33

Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions will be reported to Abbott Laboratories as serious adverse events.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone, one of the following people at Abbott Laboratories within 24 hours of being made aware of any serious adverse event.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065862

ABT-594
Protocol M99-114
February 8, 2000

34

Bruce G. McCarthy, M.D.
Associate Medical Director
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193
Office: (847) 935-6244
Home: (773) 529-5729
Fax: (847) 938-5258

Christopher J. Silber, M.D.
Venture Head
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193
Office: (847) 938-5236
Home: (847) 615-0428
Fax: (847) 938-5258

Fred Siebert
Sr. Clinical Research Associate
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193
Office: (847) 938-1167
Home: (847) 298-4682
Fax: (847) 938-5258

In addition, a written confirmation of the occurrence, including any supplementary data, must be sent within 3 days of the telephone report to:

Bruce G. McCarthy, M.D.
Dept. 48Q, Bldg. AP34
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-6193
Fax: (847) 938-5258

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study are validated and are considered standard for this population. All clinical and laboratory procedures in this study are standard and generally accepted.

9.5.3 Efficacy Variables

All efficacy variables will be derived from the efficacy measurements (Section 9.5.1.1).

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065863

ABT-594
Protocol M99-114
February 8, 2000

35

9.5.3.1 Primary Variable(s)

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variable(s)

Change from baseline to final and each scheduled evaluation will be calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert), change from baseline to each evaluation only
- Site Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health]⁴ PCS, and MCS.⁵

The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site.

9.5.4 Drug Concentration Measurements

9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay

Blood samples for ABT-594 plasma assay will be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) will be collected into a sodium heparin evacuated collection tube at each visit. Blood draws should be

ABT-594
Protocol M99-114
February 8, 2000

36

performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinue, a blood sample will be taken for ABT-594 assay at the premature discontinuation visit, and the exact times at which the dose was taken will be recorded.

All blood samples will be immediately stored at 4°C or below. The samples will be separated by centrifugation within one hour after sample collection. The supernatant will be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information will also be recorded on the appropriate CRF. All labeled plastic vials will be placed in a rack to prevent breakage. **Plasma samples for determination of ABT-594 must be frozen at -5°C or colder within one hour from centrifugation.** All specimens will be kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the day of plasma assay blood draw, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draw will be recorded in the CRF.

9.5.4.2 Additional Pharmacokinetic Sampling

For those subjects participating in the additional pharmacokinetic sampling for PK profile (approximately 30 subjects), blood samples will be collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject will be instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication will be taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit should accommodate a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples will be collected as follows: just prior to dosing (0 hour)

ABT-594
Protocol M99-114
February 8, 2000

37

and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects will receive their 8 PM dose as scheduled. Subjects will be confined at the site until the blood sample at the 8 hour time point is collected. Pharmacokinetic profile samples will be processed and stored as specified in Section 9.5.4.1 until shipment to Abbott Laboratories.

9.5.4.3 Shipment of Plasma Samples

An inventory list of the samples included in the shipment must accompany the shipment. The inventory list will include the shipping date, number of samples in the container, drug identification, Abbott protocol number, subject numbers, sample type, sampling times, and missing samples. The frozen samples will be packed in dry ice sufficient to last 2 days during shipping.

Arrangements will be made with Abbott Laboratories for shipping of the plasma samples to the following Abbott address:

Sample Receiving
Abbott Laboratories
Dept. 4TA, Bldg. AP9
100 Abbott Park Road
Abbott Park, IL 60064-6122
Phone: (847) 937-0889
Fax: (847) 938-9898

On the day of shipping, a copy of the inventory sheet should be faxed to the Sample Receiving Department at (847) 938-9898.

9.5.5 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples will be collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065866

ABT-594
Protocol M99-114
February 8, 2000

38

ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis will not be reported with the study summary. The samples may also be used for development of a diagnostic test for drug response.

The pharmacogenetic analyses involve two methods: one which examines known genes believed to be involved in the particular response (Candidate Gene), and one which uses a high density marker map to locate and identify genes related to the response (Genomic Association) by comparing the marker profile between the subjects with an effect and a corresponding negative control group. The Candidate Gene method includes genes related to drug metabolism, drug targets or target pathways, and others including genes relating to cellular homeostasis. The Genomic Association method utilizes a map of single nucleotide polymorphisms which by themselves are essentially meaningless, but when correlated with groups of two distinct subject groups allow the identification of the gene(s) related to the difference between the groups. For the purpose of pharmacogenetic studies such as this, the difference would be related to the response to the drug or the presence or absence of the disease being tested.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting will entail a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and be given a CRF completion workbook for reference. The CRAs will monitor each site approximately every 4 weeks. At each visit, 100% source-document review will be made against the entries on the CRFs and a quality-assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. The investigator must agree to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065867

PART 6

ABT-594
Protocol M99-114
February 8, 2000

39

The SF-36™ Health Status Survey (Acute) will be recorded directly on the CRF and will be considered source data.

All CRFs must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the CRFs for completeness and accuracy and sign and date the set of case report forms where indicated.

Each CRF will be printed on 3-part NCR paper. The forms consist of a white, yellow and pink copy. The white and yellow copy of the completed, verified CRF will be collected by the CRA and the pink copy retained at the investigative site.

Data captured on the CRF will be entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF will be reviewed and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values, and any necessary corrections will be made to the database and documented via addenda or audit trail.

The laboratory results will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests will be 2-tailed and considered statistically significant if the P-value (Type 1 error rate) is less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons will be made as considered necessary. No statistical adjustments will be made for multiple comparisons.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065868

ABT-594
Protocol M99-114
February 8, 2000

40

The baseline for all variables (except for the diary-based Pain Rating Scale) will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses will be performed for 2 sets of data: intent-to-treat subjects and evaluable subjects. Subjects receiving at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert) will be included in the intent-to-treat analyses. The evaluable dataset will include subjects that receive at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses will be performed with all randomized subjects who receive at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements will be assessed. The analyses will be performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation will be calculated for all efficacy variables (except both Global Impression of Change scores).

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065869

ABT-594
Protocol M99-114
February 8, 2000

41

Primary Efficacy Analysis

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable will be evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment group by study center interaction. If the interaction term is not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences will be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers have fewer than 1 subject per treatment group in the intent-to-treat dataset, data from such centers will be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert) score will be assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change will be analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS may also be analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation will be assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert). For the diary-based Pain Rating Scale (11-Point Likert), change from baseline to each scheduled evaluation will be analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change will be evaluated using CMH methodology on actual scores.

ABT-594
Protocol M99-114
February 8, 2000

42

If indicated, exploratory analyses will be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

Dose response for ABT-594 will be explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites is not significant, then the nonparametric Jonckheere-Terpstra test will be used instead of Page's test to assess dose response of ABT-594.

Other analyses will be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, will be performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses will use the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis will have data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely terminate for lack of efficacy. The "observed cases" (OC) analysis will not estimate the missing evaluation, and a subject who does not have pain evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item will be calculated, when less than one-half (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065871

ABT-594
Protocol M99-114
February 8, 2000

43

9.7.1.4 Safety Analyses

All subjects receiving at least 1 dose of study drug will be evaluated for safety.

Adverse events will be coded using the COSTART V⁶ dictionary. Treatment-emergent adverse events (i.e., those which begin or worsen in severity after randomized study drug is taken) will be tabulated by body system and COSTART term for each treatment group. Treatment group differences will be evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, will be presented for each treatment group. Analyses by subgroup will be performed as appropriate.

Laboratory data will be analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses will be on the change from baseline to the minimum, maximum and final values during the study for each laboratory variable.

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) will be summarized.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory results which satisfy the criteria for limits for statistical analysis (Appendix I) will be identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG will be analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfy the criteria for below and above limits (Appendix I) will be identified.

Concurrent medication use will be summarized by treatment group.

Additional safety analyses will be performed as indicated.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065872

ABT-594
Protocol M99-114
February 8, 2000

44

9.7.2 Determination of Sample Size

The study is designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation is based on results obtained from Study M98-833 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy⁷ and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

9.7.3 Pharmacokinetics/Pharmacodynamics

The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the trough plasma concentration (C_{trough}) will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) will be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{max} , dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{max} from the subset of subjects participating in the additional pharmacokinetic (PK) sampling will be subjected to a mixed effects model analysis. The model will include dose, visit (Visit I and Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine use status, and other variables that might account for variability in pharmacokinetics will be included as covariates. The study center factor will be included in the initial model, including a center main effect and, as appropriate, interaction of center with other factors. The center factor, or at least the interaction terms involving center, may be dropped from the model if they explain little of the variability in the data. If the number of subjects who have only Visit I data and not Visit IV data exceeds 20% of the subjects with intensive PK sampling, then analyses will also be performed for each visit separately. The hypothesis of invariance with dose will be tested by comparing the 300 µg BID dose vs the 150 µg BID dose. If the hypothesis of dose proportionality is rejected in a comparison, then the

ABT-594
Protocol M99-114
February 8, 2000

45

225 µg BID dose will be compared to each of the 150 and 300 µg BID doses. If the visit by dose interaction is statistically significant, then a comparison will be made for each visit.

An exploratory analysis will also be performed on the data set obtained from all subjects (including those who do not participate in the intensive PK sampling). This analysis will appropriately take into account the time of sampling relative to dosing. The questions of dose proportionality and change from Visit I to Visit IV will be considered in this analysis.

If there is some evidence from the data of this study that ABT-594 is efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable will be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration will utilize the data of all subjects. An analysis using only the data of subjects undergoing intensive PK sampling may also be done. The model will include effects for efficacy variable baseline value and for visit. The center factor will be incorporated appropriately. The dependency of the measurements from the same subject will be accounted for.

Other analyses may be performed as necessary.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

This study will be conducted in accordance with the protocol, GCP, all applicable local, state federal regulations and regulatory requirements. Neither the investigator nor the CRO will modify this protocol without first obtaining the concurrence of Abbott Laboratories. The modification must be documented in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the subject or those of an administrative or clarifying nature, must be reviewed and approved by the Institutional Review Board before implementation. Abbott Laboratories must submit protocol amendments to the FDA and possibly to other government agencies.

This study will be terminated if these conditions are not met.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065874

ABT-594
Protocol M99-114
February 8, 2000

46

10.0 Protocol Deviations

When deviation from the protocol is deemed necessary for an individual subject, the investigator or other physician in attendance must contact the site study monitor at the CRO, who will contact Abbott Laboratories. Such contact will be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. Any departures from the protocol will be authorized only for that one subject. A description of the departure from the protocol and the reason for it will be recorded on the CRF.

11.0 Use of Information and Publication

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 90 days before the date of submission to the intended publisher.

Neither the subject nor their physician will be informed of individual subject pharmacogenetic results, should they be performed, nor will anyone not directly involved in this research. This is due to the fact that, 1) the subject and their physician are already

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065875

ABT-594
Protocol M99-114
February 8, 2000

47

aware of the subject's particular response to the drug and the study information would not affect their future medical care, and 2) if an association is established between a genetic sequence and a treatment response, separate studies must be conducted in order to validate or confirm the results and the properties of the test prior to the necessary regulatory approval to use the test for diagnostic purposes. DNA samples from this protocol may be used either for gene identification, validation, or diagnostic test development studies, as well as discovery of genes related to painful diabetic polyneuropathy.

12.0 Completion of The Study

The investigator will complete and report this study in satisfactory compliance with the protocol within 9 months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon in writing by both the investigator and Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are not pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065876

ABT-594
Protocol M99-114
February 8, 2000

48

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

IN/R-S/1/ABT594/99114/99114PRO/P25-49
G02Q143011

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065877

PART 7

ABT-594
Protocol M99-114
February 8, 2000

49

14.0 References

1. American Academy of Pain Medicine (1997). The Use of Opioids for the Treatment of Chronic Pain. pp. 1-4.
2. **Sullivan JP and Bannon AW.** Epibatidine: pharmacologic properties of a novel nicotinic acetylcholine agonist and analgesic agent. *CNS Drug Rev.* 2(1):21-39, 1996.
3. **Sullivan JP, Briggs CA, Donnelly-Roberts D, Brioni JD, Radek RJ, McKenna DG, Campbell JE, Arneric SP, Decker MW, Bannon AW.** (+)-Epibatidine can differentially evoke responses mediated by putative subtypes of nicotinic acetylcholine receptors (nAChRs). *Med Chem Res*, 4:502-516; 1994.
4. **Ware JE.** SF-36™ Health Survey Manual and Interpretation Guide. The Health Institute, New England Medical Center, 1997.
5. **Ware JE.** SF-36™ Physical & Mental Health Summary Scales: A User's Manual. Health Assessment Lab, New England Medical Center, 1994.
6. "COSTART" Coding Symbols for Thesaurus of Adverse Reaction Terms: Fifth Edition, Department of Health and Human Services, Food and Drug Administration, Rockville, MD, 1995.
7. **Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E.** Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *JAMA.* 208(21):1831-1836, 1998.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065878

ABT-594
Protocol M99-114
February 8, 2000

50

Appendix A

Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott Laboratories has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed protocol for the study.
2. A signed Form FDA 1572 or equivalent document certifying the investigator's agreement to comply with U.S. Federal (21 CFR, ICH GCP Guidelines) regulations governing the conduct of the study.
3. A signed Abbott Financial Disclosure form.
4. A current curriculum vitae of the investigator. If sub-investigators will participate in the study, a curriculum vitae for each.
5. Requirements for the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
 - A copy of the letter of approval of the IRB/IEC. The letter must specify that both the protocol and consent form were approved.
 - The names and affiliations of the members of the IRB/IEC or assurance number.
 - If the principal and/or sub-investigator is a member of the IRB/IEC, a letter stating that he/she did not participate in the review or approval of the protocol or consent form.
6. A specimen copy of the IRB/IEC-approved informed consent document to be used in the study.
7. A list of normal ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
8. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

As a rule, these documents will be provided in the course of one or more visits to the investigator by an Abbott Laboratories representative. Usually the study cannot begin until all of the documents listed above have been provided.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065879

ABT-594
Protocol M99-114
February 8, 2000

51

Appendix B

Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,
35th World Medical Assembly, Venice, Italy, in October 1983,
41st World Medical Assembly, Hong Kong, in September 1989 and
48th General Assembly, Somerset West, Republic of South Africa 1996.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065880

ABT-594
Protocol M99-114
February 8, 2000

52

Appendix B (Cont.)

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065881

ABT-594
Protocol M99-114
February 8, 2000

53

Appendix B (Cont.)

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obligated to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.
10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065882

ABT-594
Protocol M99-114
February 8, 2000

54

Appendix B (Cont.)

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician - patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REASON FOR REVISION: Revised to correspond to the amendment adopted by the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa 1996.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065883

ABT-594
Protocol M99-114
February 8, 2000

55

Appendix C

Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott Laboratories are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is actually a form letter addressed to the sponsor (Abbott Laboratories), summarizing the investigators qualifications for the study and their willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. To secure prior approval of the study by an appropriate institutional review board which conforms to FDA regulations.
2. To make at least yearly reports on the progress of the study to the above committee, and a final report within three months of study completion.
3. To maintain current running records of the receipt, administration, and disposition of study medication and to return all unused study medication to Abbott Laboratories.
4. To obtain valid written informed consent from each patient who participates in the study.
5. To prepare and maintain adequate case histories of all persons entered into the study, including case report forms, hospital records, laboratory results, etc., and to maintain these data for a minimum of two years following notification by Abbott Laboratories that all investigations have been discontinued with this drug.
6. To identify all subinvestigators who will also supervise drug administration.
7. To report adverse effects to Abbott Laboratories promptly. In the event of serious or unexpected adverse event, to notify Abbott Laboratories immediately by telephone.
8. To allow possible inspection and copying by the FDA of case reports and records of drug distribution.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065884

ABT-594
Protocol M99-114
February 8, 2000

56

Appendix D

Elements of the Consent Form

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

For IND Studies, procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all patients participating in PPD Clinical Research studies or the patients' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of patients involved in the trial.
4. The expected duration of the patient's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The patient's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the patient and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the patient for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the patient, this should be stated.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065885

ABT-594
Protocol M99-114
February 8, 2000

57

Appendix D (Cont.)

13. The anticipated prorated payment, if any, to the patient for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
15. A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research patient's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the patient.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the patients' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the patient or the patient's legally acceptable representative is authorizing such access.
21. A statement that the site will collect information on the patient per ICH requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency will also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site.
22. A statement that the records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the patients' participation in the trial may be terminated.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065886

ABT-594
Protocol M99-114
February 8, 2000

58

Appendix D (Cont.)

24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the patient may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the consent is given to the patient.
29. The statement, "I agree to participate..."
30. A place for the patient or the patient's legally acceptable representative to sign and date.
31. A place for the person who conducted the informed consent discussion to sign and date.

PART 8

Appendix E
Sample Abbott Laboratories Drug Accountability Form
Study M99-114

ABT-594
Protocol M99-114
February 8, 2000

Subject Randomization Number: ♦ _____ Subject Initials: _____ Subject Birthdate: _____

Investigator's Name: _____ Location: _____

	Module Carton Type	Module # ♦	NPRO #	Clinical Supplies Invoice No.	Date Received (M/D/Y)
Baseline Visit	Days 1-7				
Baseline Visit	Days 8-49				
Visit II	Days 8-49				
Visit III	Days 8-49				

Visit	DISPENSED TO SUBJECT					RETURNED FROM SUBJECT			VERIFIED BY CRA	
	Module # ♦	# Capsules	Date	By*	Checked By	Date	No. of Capsules Remaining	By*	By*	Date
Baseline Visit	Days 1-7	52								

	Days 8-49	144								

Visit I	Redispose balance of Days 8-49 cards remaining from Baseline Visit	_____								
Visit II	_____	144								
Visit III	_____	144								

* Pharmacist/Coordinator/Nurse

* CRO Monitor

♦ Assigned by IVRS

59

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065888

ABT-594
Protocol M99-114
February 8, 2000

60

Appendix F

Pain Assessments

Pain Rating Scale (11 point Likert)

The subject's pain intensity will be assessed by completion of the following statement in the daily diaries and at the investigative site.

How severe was your neuropathy pain during the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Possible

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065889

ABT-594
Protocol M99-114
February 8, 2000

61

Appendix G

Neuropathic Pain Scale

Instructions: There are several different aspects of pain which we are interested in measuring: pain sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface vs. deep pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

<p>1. Please use the scale below to tell us how intense your pain is. Place an "X" through the number that best describes the intensity of your pain.</p>											
<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: left;">No pain</div> <div style="text-align: center;"> <table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="padding: 2px 10px;">0</td> <td style="padding: 2px 10px;">1</td> <td style="padding: 2px 10px;">2</td> <td style="padding: 2px 10px;">3</td> <td style="padding: 2px 10px;">4</td> <td style="padding: 2px 10px;">5</td> <td style="padding: 2px 10px;">6</td> <td style="padding: 2px 10px;">7</td> <td style="padding: 2px 10px;">8</td> <td style="padding: 2px 10px;">9</td> <td style="padding: 2px 10px;">10</td> </tr> </table> </div> <div style="text-align: right;">The most intense pain sensation imaginable</div> </div>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10	
<p>2. Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."</p>											
<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: left;">Not sharp</div> <div style="text-align: center;"> <table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="padding: 2px 10px;">0</td> <td style="padding: 2px 10px;">1</td> <td style="padding: 2px 10px;">2</td> <td style="padding: 2px 10px;">3</td> <td style="padding: 2px 10px;">4</td> <td style="padding: 2px 10px;">5</td> <td style="padding: 2px 10px;">6</td> <td style="padding: 2px 10px;">7</td> <td style="padding: 2px 10px;">8</td> <td style="padding: 2px 10px;">9</td> <td style="padding: 2px 10px;">10</td> </tr> </table> </div> <div style="text-align: right;">The most sharp sensation imaginable ("like a knife")</div> </div>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10	
<p>3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."</p>											
<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: left;">Not hot</div> <div style="text-align: center;"> <table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="padding: 2px 10px;">0</td> <td style="padding: 2px 10px;">1</td> <td style="padding: 2px 10px;">2</td> <td style="padding: 2px 10px;">3</td> <td style="padding: 2px 10px;">4</td> <td style="padding: 2px 10px;">5</td> <td style="padding: 2px 10px;">6</td> <td style="padding: 2px 10px;">7</td> <td style="padding: 2px 10px;">8</td> <td style="padding: 2px 10px;">9</td> <td style="padding: 2px 10px;">10</td> </tr> </table> </div> <div style="text-align: right;">The most hot sensation imaginable ("on fire")</div> </div>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10	
<p>4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."</p>											
<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: left;">Not dull</div> <div style="text-align: center;"> <table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="padding: 2px 10px;">0</td> <td style="padding: 2px 10px;">1</td> <td style="padding: 2px 10px;">2</td> <td style="padding: 2px 10px;">3</td> <td style="padding: 2px 10px;">4</td> <td style="padding: 2px 10px;">5</td> <td style="padding: 2px 10px;">6</td> <td style="padding: 2px 10px;">7</td> <td style="padding: 2px 10px;">8</td> <td style="padding: 2px 10px;">9</td> <td style="padding: 2px 10px;">10</td> </tr> </table> </div> <div style="text-align: right;">The most dull sensation imaginable</div> </div>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10	

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065890

ABT-594
Protocol M99-114
February 8, 2000

62

Appendix G (Cont.)

5.	Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include "like ice," and "freezing."											
Not cold	0	1	2	3	4	5	6	7	8	9	10	The most cold sensation imaginable ("freezing")
6.	Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."											
Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most sensitive sensation imaginable ("raw skin")
7.	Please use the scale below to tell us how itchy your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."											
Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most itchy sensation imaginable ("like poison oak")
8.	Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.											
Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most unpleasant sensation imaginable ("intolerable")
9.	Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.											
HOW INTENSE IS YOUR DEEP PAIN?												
No deep pain	0	1	2	3	4	5	6	7	8	9	10	The most intense deep pain sensation imaginable
HOW INTENSE IS YOUR SURFACE PAIN?												
No surface pain	0	1	2	3	4	5	6	7	8	9	10	The most intense surface pain sensation imaginable

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065891

ABT-594
Protocol M99-114
February 8, 2000

63

Appendix H

Subject Global Impression of Change and Clinician Global Impression of Change

Subject Global Impression of Change

The subject's impression of pain relief will be assessed by completion of the following statement:

Compared to the Baseline Pain Assessment Phase, how much have you changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

Clinician Global Impression of Change

The clinicians impression of pain relief will be assessed by completion of the following statement:

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to Baseline, how much has the subject changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065892

ABT-594
Protocol M99-114
February 8, 2000

64

Appendix I
Laboratory Determinations, Vital Signs and Electrocardiogram
Variables for Statistical Analysis

Hematology	Below Limit	Above Limit
Hemoglobin (g/dL)		
Female	≤ 9.5	≥ 16.5
Male	≤ 11.5	≥ 18.5
Hematocrit (%)		
Female	≤ 32	≥ 50
Male	≤ 37	≥ 55
Red Blood Cells ($\times 10^{12}/L$)		
Female	≤ 3.5	≥ 6.0
Male	≤ 3.8	≥ 7.0
White Blood Cells ($\times 10^9/L$)	≤ 2.8	≥ 16.0
Platelet Count ($\times 10^9/L$)	≤ 75	≥ 700
Eosinophils (%)		≥ 10
Basophils (%)		≥ 10
Lymphocytes (%)		≥ 75
Monocytes (%)		≥ 15
Neutrophils (%)	≤ 15	
Bands (%)		≥ 10
Mean Corpuscular Volume (fL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Mean Corpuscular Hemoglobin Concentration (g/dL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Atypical Lymphocytes (%)		≥ 5
Prothrombin Time (sec)		$\geq 2 \text{ ULN}$
Partial Thromboplastin Time (sec)		$\geq 2 \text{ ULN}$

LLN = Lower limit of normal ULN = Upper limit of normal

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065893

ABT-594
Protocol M99-114
February 8, 2000

65

Appendix I (Cont.)

Chemistry	Below Limit	Above Limit
Albumin (g/dL)	≤ 2.5	
Alkaline Phosphatase (IU/L)		$\geq 3 \times \text{ULN}$
Bicarbonate (mEq/L)	≤ 12	≥ 38
BUN (mg/dL)		≥ 30
Calcium (mg/dL)	≤ 8.2	≥ 12
Chloride (mEq/L)	≤ 90	≥ 118
Cholesterol (mg/dL)		≥ 600
Creatinine (mg/dL)		≥ 2.0
Direct Bilirubin (mg/dL)		≥ 2.0
Glucose (mg/dL)	≤ 45	≥ 175
LDH (IU/L)		$\geq 3 \times \text{ULN}$
Inorganic Phosphorus (mg/dL)	≤ 1.7	≥ 5.5
Potassium (mEq/L)	≤ 3.0	≥ 6.0
SGOT/AST (IU/L)		$\geq 3 \times \text{ULN}$
SGPT/ALT (IU/L)		$\geq 3 \times \text{ULN}$
Sodium (mEq/L)	≤ 126	≥ 156
Total Bilirubin (mg/dL)		≥ 2.0
Total Protein (g/dL)	≤ 4.5	≥ 10
Triglycerides (mg/dL)		≥ 600
Uric acid (mg/dL)		
Female		≥ 8.5
Male		≥ 10.5

ULN = Upper limit of normal

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065894

ABT-594
Protocol M99-114
February 8, 2000

66

Appendix I (Cont.)

Urinalysis	Below Limit	Above Limit
Specific Gravity	≤ 1.001	≥ 1.030
PH	≤ 4	≥ 9
Protein		$\geq 3+^*$ (≥ 10)
Ketones		$\geq 3+^*$
RBC		
Female		$\geq 10/\text{hpf}$
Male		$\geq 8/\text{hpf}$
WBC		$\geq 10/\text{hpf}$ ($\geq 2+$)
Casts		≥ 9
Glucose		$\geq 3+^*$
Oral Body Temperature		
Temperature	Low: decreased $\geq 2^\circ\text{F}$ from baseline High: $\geq 101^\circ\text{F}$	
Body Weight		
Weight	Low: decreased $\geq 15\%$ from baseline High: increased $\geq 15\%$ from baseline	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mmHg and decreased ≥ 30 from baseline High: ≥ 180 mmHg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mmHg and decreased ≥ 20 from baseline High: ≥ 105 mmHg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	

* $\geq 3+$ on a scale with 4+ being the maximum value

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065895

ABT-594
Protocol M99-114
February 8, 2000

67

Appendix I (Cont.)

Electrocardiogram	
PR Interval	High: ≥ 210 msec
QRS Duration	Low: ≤ 50 msec
	High: ≥ 150 msec
QT Interval	Low: ≤ 200 msec
	High: ≥ 500 msec
QTc Interval*	Low: ≤ 200 msec
	High: ≥ 500 msec
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline

* QTc calculated as QT divided by the square root of RR interval

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065896

Part 1

ABBOTT LABORATORIES


Clinical Study Report No. R&D/01/171

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the
Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful
Diabetic Polyneuropathy**

ABT-594/Protocol M99-114

31 July 2001

*I have read this report and confirm that to the best of my knowledge it accurately
describes the conduct and results of the study.*



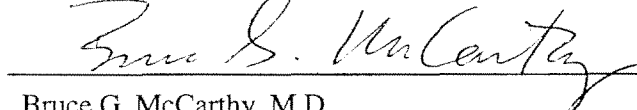
Marilyn J. Collicott
Clinical Project Manager, Analgesia Venture

01 Aug 01
Date



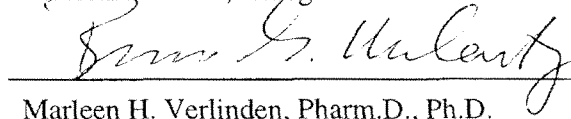
David D. Morris, Ph.D.
Assistant Director, Statistics

03 Aug 01
Date



Bruce G. McCarthy, M.D.
Medical Director, Analgesia Venture

03 Aug 01
Date

 FOR MARLEEN
VERLINDEN

Marleen H. Verlinden, Pharm.D., Ph.D.
Vice President, Global Pharmaceutical Research and
Development Neurology/Urology

03 Aug 01
Date

 **Abbott Laboratories**

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065982

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

i

1.0 Title Page

ABBOTT LABORATORIES Clinical Study Report R&D/01/171

A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy

ABT-594/Protocol M99-114

Development Phase:	II
Investigators:	Multicenter
Date First Subject Dosed:	24 April 2000
Date Last Subject Completed Dosing:	24 February 2001
Sponsor/Signatory:	Marleen H. Verlinden, Pharm. D., Ph.D. Vice President, Global Pharmaceutical Research and Development Neurology/Urology D42U, AP30 200 Abbott Park Road Abbott Park, Illinois 60064-6145 Phone: (847) 935-4096 Fax: (847) 938-1629
Report Date:	31 July 2001

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065983

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

ii

2.0 Synopsis

Name of Company: Abbott Laboratories	Individual Study Table Referring to Item of the	(For National Authority Use Only): N/A
Name of Finished Product: ABT-594 Hard Gelatin Capsule (HGC)	Submission: not applicable (N/A) Volume: N/A	
Name of the Active Ingredient: Abbott-165594	Page: N/A	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter		Study Center: Multicenter
Publication (reference): not applicable		
Study Period (years): Date First Subject Dosed: 24 April 2000 Date Last Subject Completed Dosing: 24 February 2001		Phase of Development: II
Objective: The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.		
Methodology: This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo for 49 days on an outpatient basis. Thirty-four sites were recruited in order to enroll approximately 320 subjects who met entry criteria for this study. Prior to any study-specific procedures at the Screening Visit, an informed consent was signed by the subject and study eligibility determined. Prior to study drug administration, subjects discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who met entry criteria were randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Primer Phase, subjects took BID doses of ABT-594 or placebo. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days. During the Treatment Phase, subjects returned to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). Subjects were to complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects underwent site-based assessments of their neuropathic pain at the Baseline Visit and at Treatment Visits I, II, III and IV. Subjects discontinued study drug administration after Treatment Visit IV and returned to the site for the Follow-Up Visit 7-10 days later.		

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065984

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

iii

Methodology (continued):			
During the Primer and Treatment Phases, subjects were allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but were not allowed to take acetaminophen within 24 hours prior to a Treatment Visit).			
Efficacy assessments included the Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change. Safety assessment included physical examination, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.			
No. of Subjects Planned and Enrolled:	Treatment Group	Planned	Completed/Enrolled
Planned: 320	Placebo	80	51/65
Enrolled: 266	ABT-594 150 µg BID	80	40/65
Completed: 138	ABT-594 225 µg BID	80	30/69
Premature Discontinuations: 128	ABT-594 300 µg BID	80	17/67
	TOTAL:	320	138/266
Diagnosis and Main Criteria for Inclusion:			
Adult males and females at least 18 years of age, who weighed ≤265 pounds and who were judged to be in good health based on medical history, physical examination with vital signs, laboratory profile, and 12-lead ECG, who had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit, and an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit, and who met all other selection criteria were eligible for study participation.			
Test Product, Dose and Mode of Administration, Batch Number:			
<u>Test Product</u>	<u>Dose (µg)</u>	<u>Mode of Administration</u>	<u>Drug Product Lot Numbers</u>
ABT-594 75 µg HGC,	150, 225, and	Oral	58-293-AR
Formulation A-2	300 BID		61-312-AR
Duration of Treatment: 49 days			
Reference Therapy, Dose and Mode of Administration, Batch Number:			
<u>Test Product</u>	<u>Dose (µg)</u>	<u>Mode of Administration</u>	<u>Drug Product Lot Number</u>
Placebo for ABT-594 HGC	0	Oral	55-243-AR-01
Criteria for Evaluations:			
Efficacy:			
The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation was analyzed in a similar manner. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to Day 1 of the study.			

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065985

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

iv

Criteria for Evaluations (continued):

Efficacy:

Change from baseline to final and each evaluation was calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] physical component summary (PCS), and mental component summary (MCS).

The efficacy evaluations recorded at the Baseline Visit were used as the baseline score for efficacy evaluations assessed at the investigative site.

Pharmacokinetics:

Blood samples for ABT-594 plasma assay were to be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max} , and C_{trough} were determined.

Safety:

Safety was assessed by medical history, physical exam, vital signs, ECG, clinical laboratory testing, and adverse event monitoring.

Statistical Methods:

For all safety and efficacy analyses, the primary comparisons were between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables were analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary- and site-based pain ratings were analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) were compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 was explored, with and without placebo included. Other efficacy analyses were performed as appropriate.

Treatment-emergent adverse events were summarized by body system and COSTART term and compared using Fisher's exact test.

Mean change from baseline to minimum, maximum and final values were summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits were flagged in the data listings. Furthermore, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

v

Summary/Conclusions:**Efficacy Results:**

ABT-594 at 150, 225, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Pharmacokinetic Results:

At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

Safety Results:

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065987

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

vi

Safety Results (continued):

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

Conclusions:

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

Date of Report: 31 July 2001

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

vii

3.0 Table of Contents for the Individual Clinical Study Report

	Page
1.0 Title Page.....	i
2.0 Synopsis	ii
3.0 Table of Contents for the Individual Clinical Study Report.....	vii
4.0 List of Abbreviations and Definitions of Terms	xv
5.0 Ethics	1
5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB).....	1
5.2 Ethical Conduct of the Study.....	1
5.3 Subject Information and Consent	2
5.4 Subject Confidentiality.....	2
6.0 Investigators and Study Administrative Structure.....	3
6.1 Investigative Sites.....	3
6.2 Sponsor Information.....	5
6.3 Contract Research Organization.....	5
6.4 Clinical Supply Management	5
6.5 Central Laboratory.....	6
6.6 Administrative Structure	6
7.0 Introduction	8
7.1 Analgesia Today	8
7.2 ABT-594.....	8
8.0 Study Objective	11
9.0 Investigational Plan	11
9.1 Overall Study Design and Plan: Description.....	11
9.2 Discussion of Study Design, Including the Choice of Control Groups	15
9.3 Selection of Study Population	15
9.3.1 Inclusion Criteria	15

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065989

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

viii

9.3.2	Exclusion Criteria	16
9.3.3	Removal of Subjects from Therapy or Assessment	18
9.4	Treatments	18
9.4.1	Treatments Administered.....	18
9.4.2	Identity of Investigational Product(s).....	19
9.4.2.1	Packaging and Labeling	20
9.4.2.2	Storage and Disposition of Supplies	20
9.4.2.3	Drug Accountability.....	21
9.4.3	Method of Assigning Subjects to Treatment Groups.....	21
9.4.4	Selection of Doses in the Study	22
9.4.5	Selection and Timing of Dose for Each Subject.....	22
9.4.6	Blinding	22
9.4.7	Prior and Concomitant Therapy.....	23
9.4.8	Treatment Compliance.....	23
9.5	Efficacy, Pharmacokinetic and Safety Variables.....	24
9.5.1	Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart	24
9.5.1.1	Efficacy Measurements	26
9.5.1.2	Safety Measurements and Procedures	27
9.5.2	Appropriateness of Measurements.....	35
9.5.3	Efficacy Variables.....	35
9.5.3.1	Primary Variable	35
9.5.3.2	Secondary Variables.....	35
9.5.4	Drug Concentration Measurements	36
9.5.5	Pharmacokinetic Variables	37
9.5.6	Blood Samples for Genetic Polymorphism Analysis.....	37
9.6	Data Quality Assurance.....	38
9.7	Statistical Methods Planned in the Protocol and Determination of Sample Size.....	39
9.7.1	Statistical and Analytical Plans.....	39

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065990

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

ix

9.7.1.1	Data Sets Analyzed	39
9.7.1.2	Demographic and Other Baseline Characteristics	40
9.7.1.3	Efficacy Analyses	40
9.7.1.4	Pharmacokinetic Analyses	43
9.7.1.5	Safety Analyses	44
9.7.2	Determination of Sample Size	45
9.8	Changes in the Conduct of the Study or Planned Analyses	46
9.8.1	Protocol Changes	46
9.8.2	Statistical Changes	46
10.0	Study Subjects	47
10.1	Disposition of Subjects	47
10.2	Protocol Deviations	51
11.0	Efficacy and Pharmacokinetic Evaluation	52
11.1	Data Sets Analyzed	52
11.2	Demographic and Other Baseline Characteristics	54
11.2.1	Demographics	55
11.2.2	Other Baseline Characteristics	56
11.2.3	Concurrent Medication Use	57
11.3	Measurements of Treatment Compliance	57
11.4	Efficacy Evaluations and Tabulations of Individual Subject Data	57
11.4.1	Efficacy Analyses	58
11.4.1.1	Primary Efficacy Variable	59
11.4.1.2	Secondary Efficacy Variables	60
11.4.1.3	Other Efficacy Variables	67
11.4.2	Statistical and Analytical Issues	68
11.4.2.1	Adjustments for Covariates	68
11.4.2.2	Handling of Dropouts or Missing Data	68
11.4.2.3	Interim Analyses and Data Monitoring	68

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065991

ABT-594 (ABBOTT-165594)

Study No. M99-114

x

R&D/01/171 - Clinical/Statistical

11.4.2.4	Multicenter Studies	69
11.4.2.5	Multiple Comparisons/Multiplicity.....	69
11.4.2.6	Use of an "Efficacy Subset" of Subjects	69
11.4.2.7	Active-Control Studies Intended to Show Equivalence	69
11.4.2.8	Examination of Subgroups.....	69
11.4.3	Tabulation of Individual Response Data.....	70
11.4.4	Drug Dose, Drug Concentration, and Relationship to Response	70
11.4.5	Drug-Drug and Drug-Disease Interactions	70
11.4.6	By-Subject Displays.....	70
11.4.7	Efficacy Conclusions	71
11.5	Pharmacokinetic Variables.....	71
12.0	Safety Evaluation	72
12.1	Extent of Exposure	72
12.2	Adverse Events.....	73
12.2.1	Brief Summary of Adverse Events	73
12.2.2	Display of Adverse Events.....	74
12.2.3	Analysis of Adverse Events	76
12.2.4	Listing of Adverse Events by Subject.....	77
12.3	Deaths, Other Serious Adverse Events, and Other Significant Adverse Events.....	77
12.3.1	Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events.....	78
12.3.1.1	Deaths.....	78
12.3.1.2	Other Serious Adverse Events	78
12.3.1.3	Other Significant Adverse Events	80
12.3.2	Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events.....	83
12.3.3	Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events.....	83

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065992

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xi

12.4	Clinical Laboratory Evaluation	84
12.4.1	Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value	84
12.4.2	Evaluation of Each Laboratory Parameter	85
12.4.2.1	Laboratory Values Over Time	85
12.4.2.2	Individual Subject Changes	90
12.4.2.3	Individual Clinically Significant Abnormalities	90
12.5	Vital Signs, Physical Findings, and Other Observations Related to Safety94	
12.5.1	Listing of Individual Measurements by Subject and Each Abnormal Value	94
12.5.2	Findings on Physical Examination	94
12.5.3	Vital Signs Evaluation	94
12.5.3.1	Vital Signs Values Over Time	94
12.5.3.2	Individual Subject Changes	95
12.5.4	Electrocardiogram Evaluation	96
12.5.4.1	ECG Values Over Time	96
12.5.4.2	Individual Clinically Significant Abnormalities	96
12.5.4.3	Individual Clinically Significant Abnormalities	96
12.6	Safety Conclusions	97
13.0	Discussion and Overall Conclusions	99
14.0	Tables, Figures, and Graphs Referred to but not Included in the Text	101
15.0	Reference List	
16.0	Appendices	
16.1	Study Information	
16.2	Subject Data Listings	
16.3	Case Report Forms	
16.4	Individual Subject Data Listings	

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065993

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xii

3.0 Table of Contents for the Individual Clinical Study Report (continued)

Page

List of In-Text Tables

Table 6.1a	Distribution of Subjects by Investigator and Treatment Group	4
Table 9.4a	ABT-594 Dose Escalation.....	19
Table 9.4b	Number and Type of Capsules by Treatment Group.....	19
Table 9.4c	Identity of Investigational Products.....	20
Table 9.5a	Study Procedures Flow Chart.....	25
Table 9.5b	Clinical Laboratory Tests	30
Table 10.1a	Disposition of Subjects	49
Table 11.1a	Disposition of Subjects by Dataset.....	53
Table 11.2a	Demographic Characteristics (All Treated Subjects).....	55
Table 11.2b	Other Baseline Characteristics (Intent-to-Treat Dataset)	56
Table 11.4a	Summary of the Analysis of Mean Change From Baseline ^a to Final ^b for the Average Diary-Based Pain Rating Scale ^c Scores Using LOCF Method (Intent-to-Treat Dataset).....	60
Table 11.4b	Change from Baseline to Final for Secondary Efficacy Variables ^a Using LOCF Method (Intent-to-Treat Dataset).....	62
Table 11.4c	Change from Baseline to Final for Subject and Clinician Global Impression of Change ^a Using LOCF Method (Intent-to-Treat Dataset).....	63

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065994

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xiii

Table 11.4d	Summary of the Analysis of Mean Change From Baseline ^a to Each Week for the Average Diary-Based Pain Rating Scale ^b Scores Using LOCF and OC Methods (Intent-to-Treat Dataset)	65
Table 11.4e	Proportion of Subjects Responding ^a to Treatment as Measured by Diary- and Site-Based Pain Rating Scale Scores ^b Using LOCF Method (Intent-to-Treat Dataset)	67
Table 12.1a	Extent of Exposure	72
Table 12.2a	Summary of Most Frequently Reported ^a Treatment-Emergent Adverse Events By Relationship to Study Drug	75
Table 12.3a	Subjects Reporting Serious Adverse Events During the Study	79
Table 12.3b	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects)	81
Table 12.3b	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects; continued)	82
Table 12.4a	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters	86
Table 12.4a	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters (continued)	87
Table 12.4b	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters	88

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065995

ABT-594 (ABBOTT-165594)

Study No. M99-114

xiv

R&D/01/171 - Clinical/Statistical

Table 12.4b	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters (continued).....	89
Table 12.4c	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Urinalysis Parameters	90
Table 12.4d	Number and Percentage of Subjects with Hematology Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	91
Table 12.4e	Number and Percentage of Subjects with Blood Chemistry Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	92
Table 12.4f	Number and Percentage of Subjects with Urinalysis Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	93
Table 12.5a	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Vital Sign Parameters	95
Table 12.5b	Number and Percentage of Subjects with ECG Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	97

List of In-Text Figures

Figure 6.6a	Administrative Structure	7
Figure 9.1a	Study Schematic	12
Figure 10.1a	Disposition of Subjects	50

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0065996

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xv

4.0 List of Abbreviations and Definitions of Terms

List of Abbreviations

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or Abbott-165594
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CMH	Cochran-Mantel-Haenszel
DNA	Deoxyribonucleic acid
EDTA	Edetic acid
HGC	Hard gelatin capsule
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MCS	Mental component summary
nAChR	Nicotinic acetylcholine receptor
NCR	No carbon required
NPRO	New Product Research Order
OC	Observed cases
PCS	Physical component summary
SEC	Soft elastic capsule
SF-36™	Short Form-36 Health Status Survey
SSRIs	Serotonin-specific reuptake inhibitors
TENS	Trancutaneous electrical nerve stimulation

Terms

Hemoglobin A _{1c}	Glycosolated hemoglobin
NOMAD®	A data management system

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0065997

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

1

5.0 Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator obtained a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories received documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol required IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals were required since the study was completed within 1 year. A complete list of documents required prior to initiation of the study is located in the study protocol (Appendix 16.1.1). Information regarding the IRB is presented in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version) and all applicable local regulations. The investigator ensured that the study was conducted in accordance with prevailing local laws and customs or complied with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in the study protocol (Appendix 16.1.1).

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

2

5.3 Subject Information and Consent

The investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of the Informed Consent are specified in the study protocol (Appendix 16.1.1). A sample copy of the informed consent is presented in Appendix 16.1.3.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study identified each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) were used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study were reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to ensure adequate source documentation, accuracy, and completeness of the CRFs.

The site collected information on the subject per International Conference on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who could be contacted in an emergency was also recorded. This information was treated with strict adherence to professional standards of confidentiality and was filed at the site.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

3

Neither the subject, the subject's physician, nor the investigator were informed of the subject's pharmacogenetic results, if obtained. If performed, the pharmacogenetic results from individual subjects were kept confidential and were not given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples are being stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples are being kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Thirty-four investigators in the United States were recruited to perform the study and received study drug supplies. Twenty-nine of these investigators randomized at least 1 subject. The study was conducted from 24 April 2000 to 24 February 2001. Complete names, addresses, and affiliations of the principal investigators are included in Appendix 16.1.4. The distribution of all enrolled subjects for each investigator is presented by randomized treatment group in Table 6.1a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

4

Table 6.1a Distribution of Subjects by Investigator and Treatment Group

Investigator	Total Subjects Enrolled	Treatment Group			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Backonja	3	1	1	0	1
Baumel	15	4	4	4	3
Biton	7	1	2	2	2
Bromberg	13	3	3	4	3
DeBold	12	3	3	3	3
Drucker	6	1	1	2	2
Eisner	6	1	1	2	2
Forde	2	0	0	1	1
Fried	9	2	2	3	2
Gibson	18	5	5	4	4
Gleeson	7	2	2	2	1
Haag	6	1	1	2	2
Hewitt	8	2	2	1	3
Holmlund	5	1	1	1	2
Kafka	7	2	1	2	2
Kipnes	15	4	3	4	4
Kirby	10	3	2	3	2
Kluge	9	2	2	2	3
McGill	8	2	2	2	2
Rowbotham	4	1	1	1	1
Shaibani	17	4	5	4	4
Simmons	6	1	2	2	1
Singer	15	4	4	4	3
Sivakumar	9	2	3	2	2
Steel	8	2	2	2	2
Storey	13	3	4	3	3
Suri	3	1	1	0	1
Vinik	6	2	1	2	1
Weinstein	19	5	4	5	5
Total	266	65	65	69	67

Cross Reference: Table 14.1__1.1

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066001

Part 2

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

5

6.2 Sponsor Information

The sponsor coordinated the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form were generated by Abbott Laboratories. The database for this study was created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories were responsible for the statistical analysis of the data. A copy of the signature page for the study summary with the signature of the Abbott Laboratories' responsible Medical Officer is included in Appendix 16.1.5.

6.3 Contract Research Organization

Abbott Laboratories delegated prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to the following Contract Research Organization (CRO) for the conduct of this clinical study:

Research Solutions Inc.
3200 Chapel Hill Nelson-Highway, Suite 100
P.O. Box 14561
Research Triangle Park, NC 27709
1-800-807-7462

The sponsor and CRO maintained contact in order to manage adequately the progress of the study. The CRO coordinated and performed all site visits and prepared trip reports, using the Abbott Laboratories format, for each visit performed. These reports detailed the activities conducted at all investigative sites and included all relevant observations. All trip reports were forwarded to Abbott Laboratories in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures.

6.4 Clinical Supply Management

Clinical supplies were prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories authorized the release of clinical supplies once the appropriate essential documents were received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066002

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

6

All subjects were centrally randomized by site and assigned to a treatment group (using the randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS was contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using the randomization supplied by Abbott Laboratories) was also assigned using the IVRS. Each site kept an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records, and records for return of clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) from the CRO checked drug accountability records regularly.

6.5 Central Laboratory

This study utilized 1 central laboratory. All protocol-specified clinical laboratory tests were performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214
(800) 462-8887

The ABT-594 plasma assays were performed under the supervision of Raymond Wieboldt, Ph.D. of the Drug Analysis Department of Abbott Laboratories, Abbott Park, IL.

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

7

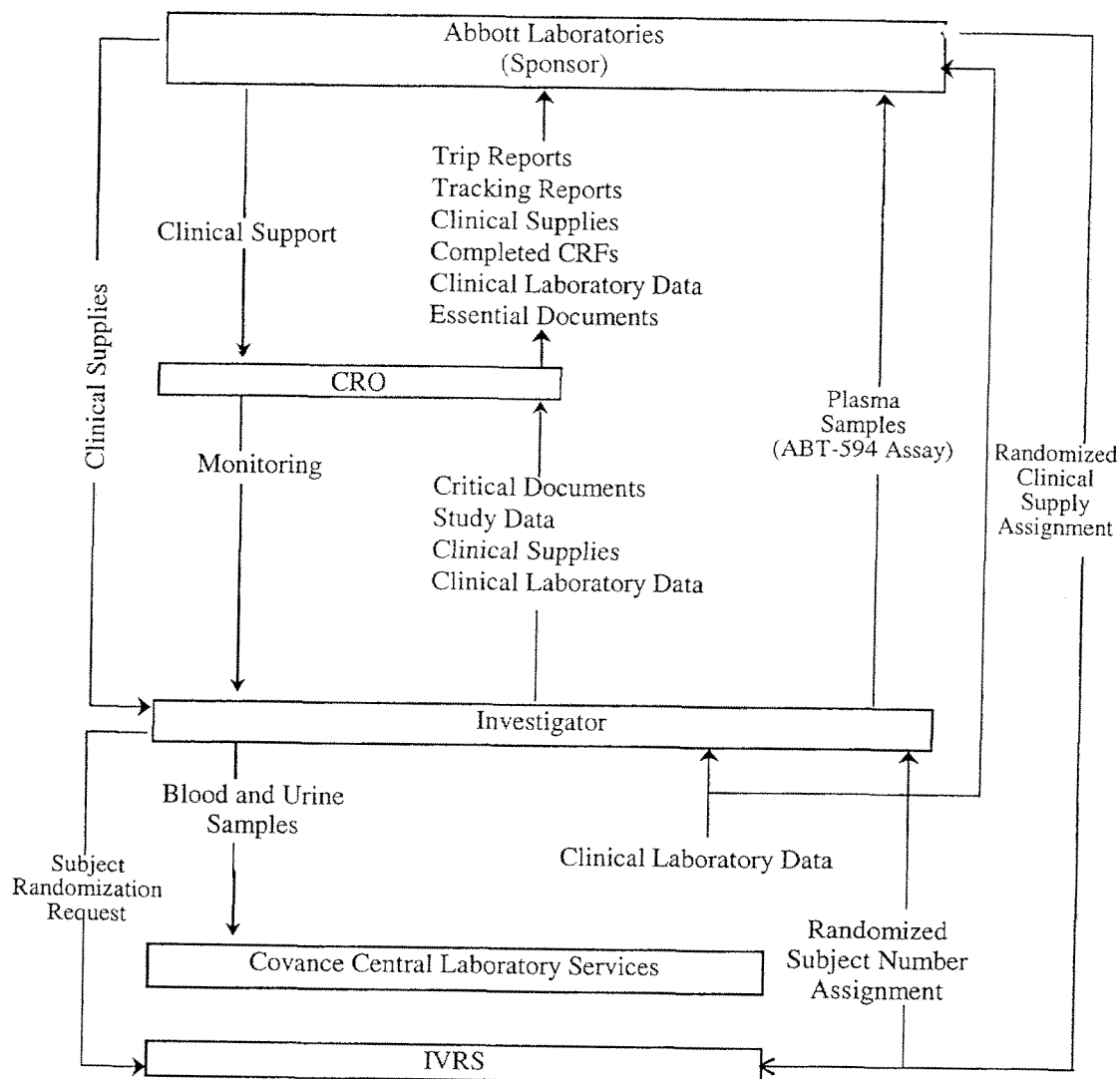


Figure 6.6a Administrative Structure

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066004

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

8

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹

Currently there are 4 major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (±)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.² The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

9

quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.³ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

Initial clinical trials in humans were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 µg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

10

solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Preliminary data from Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120⁴ included titrated doses up through 450 µg BID for 5 days. Results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout the Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

To date, Phase II trials have included efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon preliminary data from Study M97-772, a study of molar extraction pain, 100 µg ABT-594 (single-dose oral solution) appeared to be a minimally efficacious dose in acute pain.

A study of ABT-594 in osteoarthritis (M98-826)⁵ evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks, and a study of ABT-594 in neuropathic pain (M98-833),⁶ evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (≥5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature discontinuations).

Data from the Phase I and II studies completed to date suggest that ABT-594 should be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from the Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, was performed to test this hypothesis.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

11

8.0 Study Objective

The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, had an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and had ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were to be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID or placebo for 49 days on an outpatient basis. Approximately 30 sites were to be recruited in order to enroll approximately 320 subjects who met entry criteria.

The study was divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 was the first day of study drug administration. Subjects were allowed a window of ± 3 days for each study visit. A schematic of the study design is presented in Figure 9.1a.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

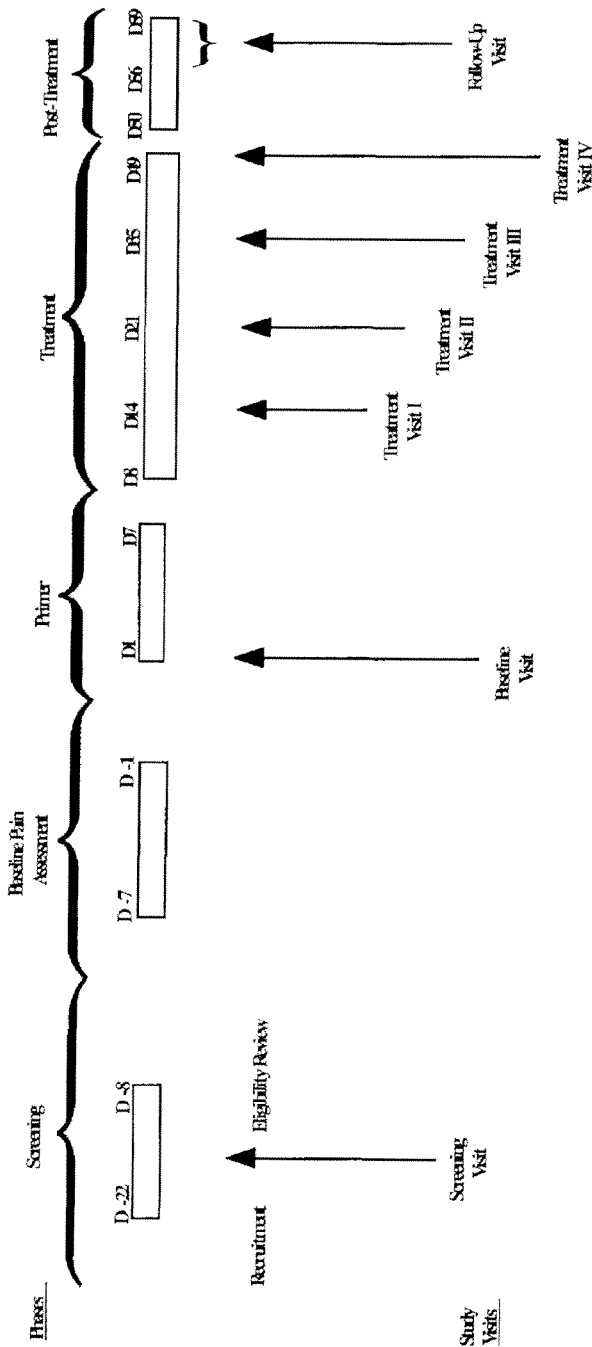


Figure 9.1a Study Schematic

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

13

Subjects reviewed and signed the informed consent prior to the conduct of any study specific procedures. Subjects were screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclic antidepressants, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs, or other analgesics for the treatment of their pain were to have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase. During the Baseline Pain Assessment Phase, at approximately 11 AM each morning, subjects were to complete the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity.

On the day after the Baseline Pain Assessment Phase, subjects returned to the site for their Baseline Visit (Day 1). At this visit, diaries were collected and reviewed. In addition, subjects were to complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who met all entry criteria, including an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, completed the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects underwent an interim medical history, physical examination, vital sign measurements, electrocardiogram (ECG), and clinical laboratory tests.

Subjects who met all entry criteria at the Baseline Visit were randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo. Subjects started study drug at the evening dose on Day 1. During the Primer Phase, subjects received a fixed dose escalation of ABT-594 or placebo (Section 9.4.1). The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days.

Throughout the course of the study, subjects were not permitted to take concomitant analgesics, except for limited doses of acetaminophen (3 grams daily maximum or 6 grams maximum during the Baseline Pain Assessment Phase, and 6 grams maximum

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

14

per week for each of the 7 weeks of the Primer and Treatment Phases; Section 9.4.7). Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of Treatment Visits I, II, III and IV.

Subjects were to complete the diary-based Pain Rating Scale each morning, 3 hours after taking their morning dose of study drug (approximately 11 AM). They returned to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV included collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III), and the following efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute; Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements, clinical laboratory tests (Treatment Visits I, III and IV), ECG (Treatment Visit IV only), and ABT-594 plasma assay collection (Treatment Visits I and IV only). A subset of subjects at selected sites underwent additional pharmacokinetic sampling at Treatment Visits I and IV.

On the day after Treatment Visit IV, subjects entered the Post-Treatment Phase. Subjects no longer took study drug or completed pain scales. Subjects could have restarted all discontinued medications under the guidance of their physician. Subjects returned for study procedures at the Follow-Up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-Up Visit included physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV, and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participated in clinical studies of ABT-594 and who consented, a blood sample was collected in order to obtain a sample of genetic material (deoxyribonucleic acid [DNA]). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066011

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

15

genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

Copies of the protocol and amendment, and the CRF are included in Appendices 16.1.1 and 16.1.2, respectively.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provided a placebo-control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel-group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales were employed.

9.3 Selection of Study Population

Approximately 320 subjects were to be randomized and receive study medication in this study. A subject was randomized in this study provided that he/she met all of the inclusion criteria outlined in Section 9.3.1 and did not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

A subject was to meet all of the following criteria within 22 days before the initial dose of study drug:

1. Prior to any study specific procedure, voluntary written informed consent was obtained from the subject after the purpose and nature of the study were explained.
2. The subject was age 18 or older and in relatively good health with a recent stable medical history.
3. The subject's weight was ≤ 265 pounds.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

16

4. A female subject was to be non-lactating and:
 - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation), or
 - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and continued the contraceptive method through the course of the study).

All female subjects had a negative β subunit human chorionic gonadotropin (β -hCG) at the Baseline Visit. Female subjects of childbearing potential had a negative β -hCG at all Treatment Visits.

5. The subject had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, and good control (in the opinion of the investigator) of the subject's serum glucose for at least the last 3 months prior to the Screening Visit.
6. The subject had distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.
7. The location and quality of the pain under study were consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
8. The subject had distal symmetric diabetic polyneuropathy symptoms (including pain) which were stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
9. The subject had an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

A subject was to be excluded from participation in the study for any of the following reasons:

1. The subject had a positive test result for drugs of abuse or viral hepatitis at the Screening Visit, or had a known history of a positive test result for HIV.
2. The subject had recent (< 5 years) history of drug or alcohol abuse or dependence.
3. The subject had an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066013

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

17

4. The subject had an active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that had been treated or other malignancies that had been surgically removed and had no evidence of recurrence for a minimum of 5 years prior to study start).
5. The subject had taken an investigational drug within 1 month prior to administration of study treatment or was scheduled to receive an investigational drug other than ABT-594 during the course of this study.
6. The subject had a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.
7. The subject had orthostatic hypotension (defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing) at the Screening Visit, or a history of syncope or pre-syncope symptoms.
8. The subject had previously participated in a study involving ABT-594, including the present study.
9. The subject had clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of the reference range, a serum creatinine >1.5 mg/dL or a hemoglobin A_{1c} $>11\%$ (subjects may have had elevated serum and urine glucose).
10. The subject had clinically significant electrocardiographic abnormalities.
11. The subject had ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.
12. The subject had a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject could not differentiate from the neuropathy pain.
13. The subject had sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.
14. The subject was unlikely to comply with the study protocol or was unsuitable for any other reason, in the opinion of the investigator.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066014

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

18

9.3.3 Removal of Subjects from Therapy or Assessment

A subject could have voluntarily discontinued participation in the study at any time. The investigator may also have decided, for medical reasons or protocol noncompliance, to discontinue prematurely a subject's participation. The investigator was to notify the CRA within 24 hours and document the reason for premature discontinuation on the appropriate CRF.

Subjects whose participation was discontinued prematurely after signing study consent but before study drug administration did not require follow-up observations. Subjects whose participation was discontinued prematurely after study drug administration were to undergo the procedures normally performed at Treatment Visit IV within 7 to 10 days following discontinuation from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represented a significant risk to subjects, the study was to be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID
ABT-594 225 µg BID
ABT-594 300 µg BID
Placebo for ABT-594 BID

ABT-594 and matching placebo were supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects received a fixed dose escalation of study drug. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4a.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066015

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

19

Table 9.4a ABT-594 Dose Escalation

Treatment Group	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594 BID	8 AM	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594 BID	8 AM	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg	225 µg
300 µg ABT-594 BID	8 AM	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg	300 µg
	8 PM	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg	300 µg

During the Primer Phase, subjects randomized to placebo received a fixed dose escalation of placebo BID, in a double-blind fashion.

Subjects started study drug at the PM dose on Day 1 (Section 9.4.5). The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4b.

Table 9.4b Number and Type of Capsules by Treatment Group

Treatment Group	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg BID	2	2
ABT-594 225 µg BID	3	1
ABT-594 300 µg BID	4	0
Placebo BID	0	4

9.4.2 Identity of Investigational Product(s)

Information regarding the formulations used in this study is presented in Table 9.4c.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066016

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

20

Table 9.4c Identity of Investigational Products

Test Preparation	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR 61-312-AR	52-015-KD-00	Abbott ^a
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	not applicable	Abbott ^a
^a PARD Solids Pilot Plant, North Chicago, Illinois.			

The ABT-594 75 µg HGC and placebo HGC were identical in appearance.

A listing of subjects receiving test preparations/investigational products from specific batches is presented in Appendix 16.1.6.

9.4.2.1 Packaging and Labeling

Study drug supplies were blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards were provided to each subject.

Daily study medication cards were labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space was provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies were stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies were stored at controlled room temperature (68-77° F, see USP).

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066017

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

21

9.4.2.3 Drug Accountability

The investigator or designee verified that study drug supplies were received intact and in the correct amounts. This was documented by signing and dating the Clinical Supplies Invoice or similar document. Study drug was dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who met the enrollment criteria. The investigator or designee recorded the subject number, subject initials, and date the study drug was dispensed to the subject on the Abbott Laboratories Drug Accountability Form. The amount of study drug remaining was recorded at Treatment Visits I, II, III and IV for each subject on the M99-114 Final Drug Supply Reconciliation Summary by Investigator Form. An accurate running inventory of study drug was kept and included the NPRO number, Clinical Supplies Invoice number(s), the number of modules dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug was performed and verified by the CRA throughout the study and at the site close-out visit. All supplies (unused and empty blister cards) were inventoried, accounted for, and returned to Abbott Laboratories. A copy of the Return of Investigational Drug Supplies for Disposal Form, in accordance with the instructions of the CRA, was also included in the shipment. The investigator agreed not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule was computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects were centrally randomized by investigative site using an IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site.

Approximately 320 subjects were to be randomized in an equal ratio to receive either ABT-594 150 µg, 225 µg, 300 µg BID or placebo. Subjects were assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

The randomization schedule is presented in Appendix 16.1.7.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

22

9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects started study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects then took BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs were to be taken with at least 1 cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject remained blinded to the subject's treatment throughout the course of the study. The study blind may have been broken if, in the opinion of the investigator, it was in the subject's best interest to know the study drug assignment. The sponsor was to be notified before breaking the blind, unless identification of the study drug was required for emergency therapeutic measures. Blind breaking information was to be provided using IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site. The sponsor was to be notified within 48 hours of the blind being broken. The date and reason for blind breakage were to be recorded on the appropriate CRF.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

23

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks was taken.

Concomitant analgesics (prescription or over-the-counter [OTC], except aspirin and acetaminophen as described below), including (but not limited to) serotonin-specific reuptake inhibitors, mixed serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, NSAIDs, COX-2 inhibitors, muscle relaxants, transcutaneous electrical nerve stimulation (TENS) and topical analgesics were not allowed. In addition, St. John's Wort was not allowed.

Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, was permitted. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication was necessary during the course of this study, the medication name, dosage information, frequency and dates of administration was reported on the CRF. Concomitant analgesic medication use (frequency only) was recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and at Treatment Visits I, II, III and IV. The concomitant medication use record included the number of separate occasions each subject had used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects were instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance was documented by the investigator or designee on the M99-114 Final Drug Supply Reconciliation Summary by

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066020

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

24

Investigator Form and on the appropriate CRF. Overdose information was collected on the appropriate CRF.

9.5 Efficacy, Pharmacokinetic and Safety Variables

9.5.1 Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Study procedures were performed as summarized in Table 9.5a, Study Procedures Flow Chart.

Part 3

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

25

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7	Treatment Phase D8-D49				Post-Treatment Phase D50-D59	
				Treatment Visit					
				D8-D49	D14 I	D21 II	D35 III		D49 IVa
Screening Visit		D-7 to D-1	Baseline Visit D1	D2-D7					Follow-Up Visit D56 to D59
Informed Consent	X								
Medical History	X		X ^b						
Physical Exam	X ^c		X					X	X
Vital Signs	X ^d		X ^e			X		X	X
ECG			X					X	X ^f
Clinical Laboratory Tests ^g	X		X					X	X ^f
Viral Hepatitis Screen	X								
Urine Drug and Alcohol Screen	X								
Pregnancy Test			X				X ^h	X ^h	X ^h
Genetic Polymorphism Sample (If Applicable)			X						
ABT-594 Plasma Assay			X				X		X
ABT-594 Pharmacokinetic Profile ⁱ							X		X
Diary Issued	X		X				X	X	
Diary Collected			X		X		X	X	
Diary-Based Pain Rating Scale ^j		X							
Site-Based Pain Rating Scale									
Neuropathic Pain Scale			X				X	X	
Subject/Clinician Global Impression of Change			X				X	X	
SF-36 TM			X						X
Randomize Subject			X						
Dispense Study Drug			X						
Analgesic Use Monitoring							X ^k	X	
Adverse Event Monitoring			X				X	X	
Concomitant Medication Monitoring			X				X	X	X
Study Drug Accountability			X				X	X	X

^a Or upon premature discontinuation.

^b Interim history.

^c Included height.

^d Included orthostatic measurements at Screening Visit only.

^e Included oral temperature at Baseline Visit only.

^f Performed only if there were clinically significant abnormalities at the previous evaluation.

^g Chemistry, hematology and urinalysis.

^h Required of all females of child-bearing potential.

ⁱ Study drug was to be taken in front of study staff. Blood samples from selected subjects were taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.

^j To be completed at approximately 11 AM each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.

^k Redispensed study medication for days 15-20 after checking drug accountability.

^a Or upon premature discontinuation.

^b Interim history.

^c Included height.

^d Included orthostatic measurements at Screening Visit only.

^e Included oral temperature at Baseline Visit only.

^f Performed only if there were clinically significant abnormalities at the previous evaluation.

^g Chemistry, hematology and urinalysis.

^h Required of all females of child-bearing potential.

ⁱ Study drug was to be taken in front of study staff. Blood samples from selected subjects were taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.

^j To be completed at approximately 11 AM each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.

^k Redispensed study medication for days 15-20 after checking drug accountability.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066022

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

26

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer instructed the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) was the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments included the diary- and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements were to be performed 3 to 4 hours post dose, when possible.

Pain Rating Scale (11-Point Likert Scale)

Subjects were to assess pain intensity daily by completing the Pain Rating Scale in their diaries. These assessments were to be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects were to record the time they completed the assessments in their diaries.

Subjects also were to assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments were to be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation). The time of assessment was recorded on the appropriate CRF.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

27

Neuropathic Pain Scale

The Neuropathic Pain Scale was completed by subjects at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation).

Subject Global Impression of Change

The Subject Global Impression of Change of analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

Clinician Global Impression of Change

The Clinician Global Impression of Change of a subject's analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) was completed by each subject at the Baseline Visit and at Treatment Visit IV (or upon premature discontinuation).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative explained the nature of the study to the subject and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

28

Medical History

A complete medical history was obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening was recorded. The medical history was updated at the Baseline Visit.

Physical Examination

A physical examination, including weight, was performed at the Screening Visit, Baseline Visit, Treatment Visit IV, and Follow-Up Visit. Height was measured at the Baseline Visit only. The physical examination performed at the Baseline Visit served as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate were measured at the Screening Visit, Baseline Visit, Treatment Visits I, III, and IV, and Follow-Up Visit. Orthostatic blood pressure and pulse rate were measured at the Screening Visit only. Oral temperature was taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit served as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) were obtained after the subject had been sitting for at least 3 minutes. Orthostatic measurements were obtained after 3 minutes in the supine position and then after 1 minute in the standing position. Ideally, the subject's blood pressure was to be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurements were to precede, not follow, scheduled blood draws. Subjects were kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

29

Electrocardiogram (ECG)

A resting 12-lead ECG was obtained at the Baseline Visit and at Treatment Visit IV. An ECG was performed at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The ECG performed at the Baseline Visit served as the baseline ECG.

A qualified physician interpreted the ECG. One copy of each 12-lead ECG and physician's report was retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples were obtained for the clinical laboratory tests presented in Table 9.5b at the Screening Visit, Baseline Visit, and Treatment Visits I, III, and IV. Laboratory tests were obtained at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The laboratory test results obtained at the Baseline Visit served as the baseline results (except for hemoglobin A_{1c}, for which the result obtained at the Screening Visit was used as the baseline result). Blood draws were to be performed after pain assessments or vital sign determinations during a visit.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

30

Table 9.5b Clinical Laboratory Tests

Hematology	Blood Chemistry	Urinalysis
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total Bilirubin	pH
White Blood Cell (WBC) count	Aspartate Aminotransferase/ Serum Glutamic-Oxaloacetic Transaminase (AST/SGOT)	Bilirubin
Neutrophils	Alanine Aminotransferase/ Serum Glutamic-Pyruvic Transaminase (ALT/SGPT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline Phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Lymphocytes	Chloride	
Hemoglobin A _{1c} (Screening Visit and Treatment Visit IV only)	Calcium	
Mean Corpuscular Hemoglobin (MCH)	Inorganic Phosphorus	
Mean Corpuscular Hemoglobin Concentration (MCHC)	Uric Acid	
Mean Corpuscular Volume (MCV)	Bicarbonate	
Platelet count (estimate was not acceptable)	Cholesterol	
Prothrombin Time (PT)	Total Protein	
Partial Thromboplastin Time (PTT)	Glucose	
	Triglycerides	
	Albumin	

A central laboratory was utilized to process and provide results for the clinical laboratory tests.

The investigator reviewed all laboratory test results and assessed the clinical significance for each abnormal result. All laboratory test results that were considered clinically significant by the investigator were followed to satisfactory resolution. A copy of each laboratory report was included with the CRF.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

31

Viral Hepatitis Screen

At the Screening Visit, subjects underwent serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody). The hepatitis test panel was performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens, collected at the Screening Visit, were tested for drugs of abuse and alcohol by the central laboratory.

Pregnancy Test

A urine pregnancy test was performed by designated study personnel at the Baseline Visit for all female subjects and at Treatment Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female was not eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected event(s) such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject. Subjects were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken.

All adverse events, whether in response to a query, observed by site personnel, or spontaneously reported by the subject were reported on the appropriate CRF. All adverse events and post-treatment laboratory abnormalities considered clinically significant by the investigator were followed to a satisfactory resolution.

The investigator assessed and recorded any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known),

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

32

severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must have been of a similar nature and severity.

The investigator used the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator used the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly related, probably not related, or not related to study drug was given, an alternate etiology was provided for the adverse event.

Adverse events (including those that met regulatory criteria for a serious adverse event) were monitored continuously from the time of study drug administration to the

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

33

Follow-Up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature discontinuation) were collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects were instructed to report to the investigator any other adverse events that occurred after the Follow-Up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures, that occurred after signing the informed consent and prior to the first dose of study drug were also collected.

Any abnormal laboratory value or change in vital signs was not documented as an adverse event unless it was a reason for premature discontinuation from the study, required treatment, or met regulatory criteria for a serious adverse event.

Ongoing medical conditions were considered adverse events if there was an increase in severity or frequency of occurrence. Since measurements of pain intensity were efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study was not considered an adverse event for the purposes of this study.

Serious Adverse Events

If an adverse event met any of the following criteria, whether related to study drug or not, the investigator and other professional personnel in attendance was to be notified as soon as possible for the appropriate action. The investigators were to notify Abbott Laboratories by telephone within 24 hours of being made aware of any serious adverse event. In addition, a written confirmation of the occurrence, including any supplementary data, was to be sent within 3 days of the telephone report.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

34

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions were to be reported to Abbott Laboratories as serious adverse events.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

35

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study were validated and considered standard for this population. All clinical and laboratory procedures in this study were standard and generally accepted.

9.5.3 Efficacy Variables

9.5.3.1 Primary Variable

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variables

Change from baseline to final and each scheduled evaluation was calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each evaluation only
- Site-based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health]⁷ physical component summary (PCS), and mental component summary (MCS).⁸

The pain evaluations recorded at the Baseline Visit were used as the baseline score for pain evaluations assessed at the investigative site.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

36

9.5.4 Drug Concentration Measurements

Blood samples for ABT-594 plasma assay were to be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) was to be collected into a sodium heparin evacuated collection tube at each visit. Blood draws were to be performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinued, a blood sample was to be taken for ABT-594 assay at the premature discontinuation visit, and the exact time at which the prior dose was taken was to be recorded.

For those subjects participating in the additional pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), blood samples were collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject was instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication was taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit accommodated a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples were collected as follows: just prior to dosing (0 hour) and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects received their 8 PM dose as scheduled. Subjects were confined at the site until the 8-hour blood sample was collected.

All blood samples were immediately stored at 4°C or below. The samples were to be separated by centrifugation within 1 hour after collection. The supernatant was to be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information was also recorded on the appropriate CRF. All labeled plastic vials were placed in a rack to prevent breakage. Plasma samples for determination of ABT-594 were frozen at -5°C or colder within

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

37

1 hour from centrifugation. All specimens were kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the days of plasma assay blood draws, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draws were recorded on the CRF.

Details of the ABT-594 assay methodology will be presented in the Clinical Pharmacokinetic Report.

9.5.5 Pharmacokinetic Variables

For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max} , and C_{trough} were to be calculated using noncompartmental methods.

9.5.6 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples were collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to Covance Central Laboratory Services.

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis are not reported with this study summary. The samples may also be used for development of a diagnostic test for drug response.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

38

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting was held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting entailed a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site were trained on the study procedures by a CRA at a study initiation visit and given a CRF completion workbook for reference. The CRAs monitored each site approximately every 4 weeks. At each visit, 100% source-document review was made against the entries on the CRFs and a quality-assurance check was performed to ensure that the investigator was complying with the protocol and regulations. The investigator agreed to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs were retrieved by the CRA, a review of the data was conducted by a physician and a clinical review team at Abbott Laboratories.

The SF-36™ Health Status Survey (Acute) was recorded directly on the CRF and was considered source data.

All CRFs were to be legible and completed in black ball point ink. All corrections were initialed and dated by the investigator or designated assistant. The investigator reviewed the CRFs for completeness and accuracy and signed and dated the set of CRFs where indicated.

Each CRF was printed on 3-part no carbon required (NCR) paper. The forms consisted of a white, yellow and pink copy. The white and yellow copies of the completed, verified CRF were collected by the CRA and the pink copy was retained at the investigative site.

Data captured on the CRF were entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF were reviewed and corrected on-line. After completion of the entry process, computer logic checks were run to check for such items as inconsistent study dates and outlying laboratory values, and

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

39

any necessary corrections were made to the database and documented via addenda or audit trail.

The laboratory results were electronically transferred from the central laboratory to the study database. A final review of all laboratory results was conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests were 2-tailed and considered statistically significant if the P-value (Type 1 error rate) was less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest were between each ABT-594 treatment group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons were to be made as considered necessary. No statistical adjustments were made for multiple comparisons.

The baseline for all variables (except for the diary-based Pain Rating Scale) was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to the subject receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses were to be performed for 2 sets of data: intent-to-treat (ITT) subjects and evaluable subjects. Subjects who received at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale) were included in the ITT

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

40

analyses. The evaluable dataset included subjects who received at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses were performed with all randomized subjects who received at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements was assessed. The analyses were performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation was calculated for all efficacy variables (except both Global Impression of Change scores).

Primary Efficacy Analysis

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable were evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

41

group by study center interaction. If the interaction term was not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences was to be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers had fewer than 1 subject per treatment group in the ITT dataset, data from such centers were to be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert Scale) score were assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change were analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS could have also been analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation were assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert Scale). For the diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each scheduled evaluation was analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change was evaluated using CMH methodology on actual scores.

If indicated, exploratory analyses were to be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

42

Dose response for ABT-594 was explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites was not significant, then the nonparametric Jonckheere-Terpstra test was to be used instead of Page's test to assess dose response of ABT-594.

Other analyses were to be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, were performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely discontinue for lack of efficacy. The "observed cases" (OC) analysis did not estimate the missing evaluation, and a subject who did not have pain evaluation on a scheduled visit was excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item was calculated, when less than ½ (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

43

9.7.1.4 Pharmacokinetic Analyses

The maximum observed plasma concentration (C_{\max}), the time to C_{\max} (T_{\max}), and the trough plasma concentration (C_{trough}) were to be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) were to be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{\max} , dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{\max} from the subset of subjects participating in the additional pharmacokinetic sampling were to be subjected to a mixed effects model analysis. The model was to include dose, visit (Treatment Visit I and Treatment Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine-use status, and other variables that may have accounted for variability in pharmacokinetics were to be included as covariates. The study center factor was to be included in the initial model, including a center main effect and, interaction of center with other factors. The center factor, or at least the interaction terms involving center, were to be dropped from the model if they explained little of the variability in the data. If the number of subjects who had only Treatment Visit I data and not Treatment Visit IV data exceeded 20% of the subjects with additional pharmacokinetic sampling, then the analyses were also to be performed for each visit separately. The hypothesis of invariance with dose was to be tested by comparing the 300 μg BID dose versus the 150 μg BID dose. If the hypothesis of dose proportionality was rejected in a comparison, then the 225 μg BID dose was to be compared to each of the 150 and 300 μg BID doses. If the visit by dose interaction was statistically significant, then a comparison was to be made for each visit.

An exploratory analysis was also to be performed on the data set obtained from all subjects (including those who did not participate in the additional pharmacokinetic sampling). This analysis was to take into account the appropriate time of sampling

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

44

relative to dosing. The questions of dose proportionality and change from Treatment Visit I to Treatment Visit IV were to be considered in this analysis.

If there was some evidence from the data of this study that ABT-594 was efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable was to be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration was to utilize the data of all subjects. An analysis using only the data of subjects undergoing additional pharmacokinetic sampling was also to be performed. The model was to include effects for efficacy variable baseline value and for visit. The center factor was to be incorporated appropriately. The dependency of the measurements from the same subject was to be accounted for. Other analyses were to be performed as necessary.

9.7.1.5 Safety Analyses

All subjects who received at least 1 dose of study drug were evaluated for safety.

Adverse events were coded using the COSTART V9 dictionary. Treatment-emergent adverse events (i.e., those which began or worsened in severity after randomized study drug was taken) were tabulated by body system and COSTART term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, was presented for each treatment group. Analyses by subgroup were performed as appropriate.

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the change from baseline to the minimum, maximum, and final values during the study for each laboratory variable.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

45

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) was summarized.

Laboratory data values were categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values were flagged in the data listings. In addition, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG were analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfied the criteria for below and above limits were identified.

Concurrent medication use was summarized by treatment group.

Additional safety analyses were to be performed as indicated.

9.7.2 Determination of Sample Size

The study was designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size should have allowed for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation was based on results obtained from Study M98-8336 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy¹⁰ and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

46

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

Significant changes in the developmental strategy of ABT-594 resulted in the study being prematurely discontinued by the sponsor. Therefore, although the protocol specified that approximately 320 subjects (80 per treatment group) were to be enrolled, enrollment was stopped at 266 subjects.

The final clinical protocol incorporated Amendment Number 1. All subjects were enrolled under the final protocol (Table 14.1__2). Full details of the clinical protocol and its amendment are presented in Appendix 16.1.1. Important changes included in the amendment are summarized below:

Amendment 1 (29 February 2000)

- Modified the inclusion criteria such that subjects were required to have good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit.
- Added that subjects with a hemoglobin A_{1c} >11% were to be excluded.
- Added hemoglobin A_{1c} at the Screening Visit and Treatment Visit IV and deleted the hemoglobin A_{1c} at the Baseline Visit.
- Added mixed serotonin and norepinephrine reuptake inhibitors and St. John's Wort to the list of excluded medications.
- Added that the Screening hemoglobin A_{1c} result served as the baseline result.

9.8.2 Statistical Changes

Although not specified in the protocol, efficacy analyses were also performed on a dataset that included subjects who did not prematurely discontinue from the study (study completers).

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

47

The change from baseline of the average diary-based Pain Rating score from each subject's diary to the corresponding average of each of the consecutive 7-day intervals after the first dose of study drug was summarized using both LOCF and OC techniques.

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to final, was analyzed for the following variables: diary- and site-based average Pain Rating Scale scores and Neuropathic Pain Scale Total Scores. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

10.0 Study Subjects

10.1 Disposition of Subjects

The location of premature discontinuation data is presented below.

Assessment	Statistical Analyses Table	Individual Subject Listing Appendix
Number and Percentage of Subjects Prematurely Discontinued	14.1__3.1	16.2__1.1
Listing of Subject Numbers by Reason for Premature Discontinuation	14.1__3.2	16.2__1.1
Subjects Who Prematurely Discontinued and Any Adverse Events for Which Study Drug was Prematurely Discontinued	14.1__3.3	16.2__1.1 16.2__7.1.1
Number of Subjects Who Prematurely Discontinued by Days of Exposure to Study Drug	14.1__3.4	16.2__1.1 16.2__5.1.1 16.2__5.1.2
Number and Percentage of Subjects that Prematurely Discontinued for Each Investigator	14.1__3.5	16.2__1.1
Previous and Concurrent Medications (Subjects Who Prematurely Discontinued)	none	16.2__1.1 16.2__1.2

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066044

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

48

Two hundred sixty-six (266) subjects were enrolled by 29 investigators. Of the 266 subjects, 65 were randomized to receive placebo, 65 were randomized to receive ABT-594 150 µg BID, 69 were randomized to receive ABT-594 225 µg BID, and 67 were randomized to receive ABT-594 300 µg BID. All 266 subjects who received study drug are included in the analyses of all treated subjects. Additionally, 3 subjects were randomized although they failed to meet admission criteria. These subjects did not receive study drug and are not included in the database.

The proportion of subjects prematurely discontinuing from the study was statistically significantly different among the treatment groups, with 14 (22%) subjects in the placebo treatment group, 25 (38%) subjects in the ABT-594 150 µg BID treatment group, 39 (57%) subjects in the ABT-594 225 µg BID treatment group, and 50 (75%) subjects in the ABT-594 300 µg BID treatment group. A statistically significant difference was also observed among the treatment groups for the proportion of subjects prematurely discontinuing from the study due to 1 or more adverse event, which was the most frequently reported reason for premature discontinuation (9% placebo, 28% ABT-594 150 µg BID, 46% ABT-594 225 µg BID, and 66% ABT-594 300 µg BID). Subject disposition is presented in Table 10.1a.

Part 4

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

49

Table 10.1a Disposition of Subjects

	Treatment Group n (%)			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
All Treated Subjects	65	65	69	67
Completed Study	51 (78%)	40 (62%)	30 (43%)	17 (25%)
Prematurely Discontinued ^a	14 (22%)	25 (38%)	39 (57%)	50 (75%)
Adverse Event	6 (9%)	18 (28%)	32 (46%)	44 (66%)
Lack of Efficacy	6 (9%)	6 (9%)	2 (3%)	5 (7%)
Withdrew Consent	2 (3%)	3 (5%)	6 (9%)	5 (7%)
Subject Noncompliant	1 (2%)	3 (5%)	4 (6%)	2 (3%)
Lost to Follow-up	0	0	1 (1%)	2 (3%)
Other ^b	1 (2%)	1 (2%)	3 (4%)	2 (3%)
^a Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.				
^b Description of reason designated as "other": subject stopped taking study drug (2 subjects), initiation of exclusionary medication, medical records noting subject is an alcoholic, refusal to return for follow-up, out of town for 6 weeks, and randomization error (1 subject each).				

Cross Reference: Tables 14.1__3.1 and 14.1__3.3 and Appendix 16.2__1.1

A graphic disposition of all subjects is presented in Figure 10.1a.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

50

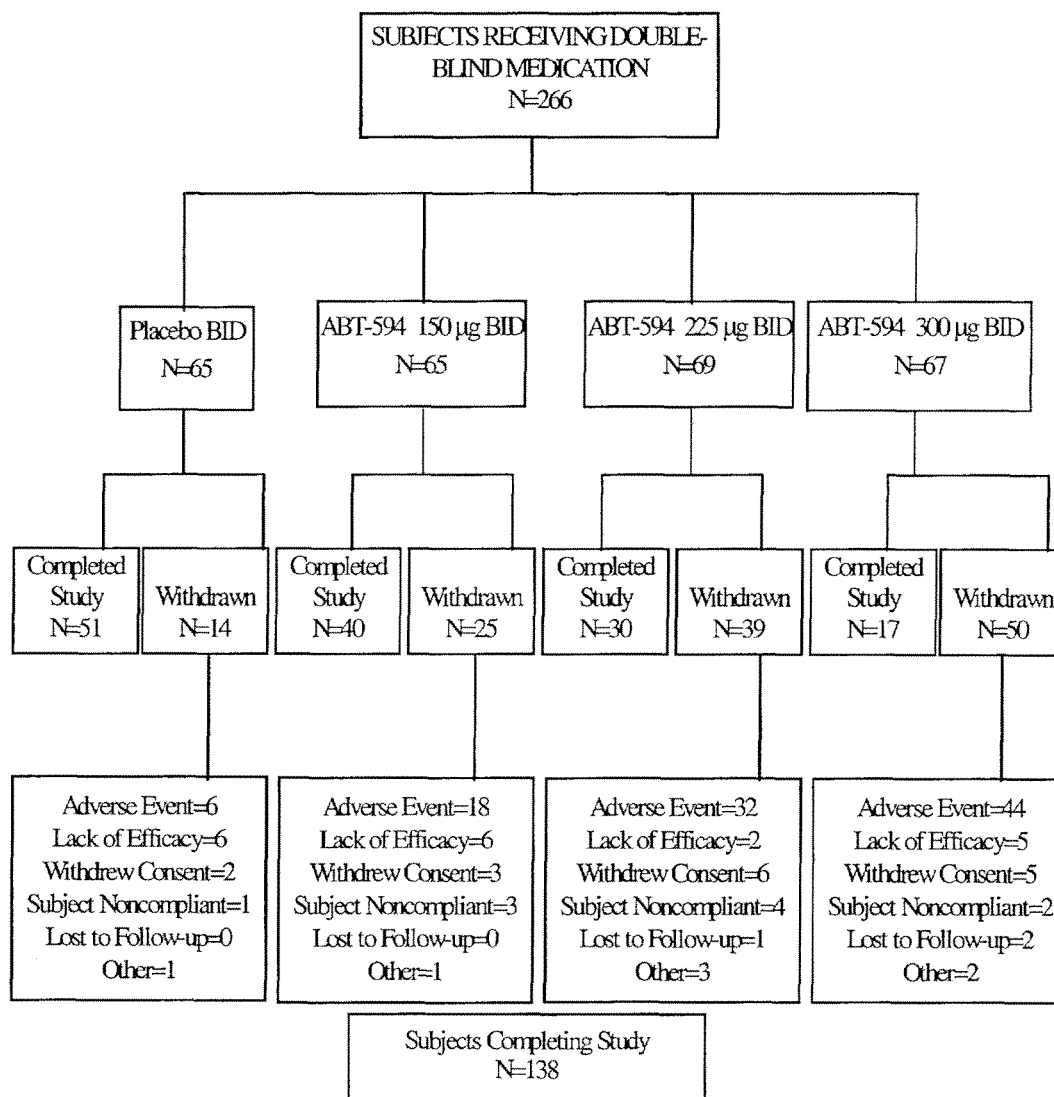


Figure 10.1a Disposition of Subjects

Note: Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

51

10.2 Protocol Deviations

The location of protocol deviation data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Admission Criteria	none	16.2__2.1
Blind Broken	none	16.2__1.3
Urine Drug Screen	none	16.2__2.2
Hepatitis Screen	none	16.2__2.3
Pregnancy Test Results	none	16.2__2.4
Other Medications and Supplements	none	16.2__7.3

In reviewing the data for all subjects, deviations from the protocol were identified. Clinically significant inclusion/exclusion criteria deviations included the following: failure to perform a pregnancy test at the Baseline Visit (19 subjects), current or expected use of an exclusionary medication (10 subjects), failure to have an average of ≥ 4 points on the diary-based Pain Rating Scale during the Baseline Pain Assessment Phase and ≥ 4 points on the site-based Pain Rating Scale at the Baseline Visit (6 subjects), acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness (2 subjects), and failure to have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy (2 subjects). These and other minor deviations were not considered important enough to affect the outcome of the study.

One hundred twenty (15 placebo, 30 ABT-594 150 μg , 34 ABT-594 225 μg , and 41 ABT-594 300 μg BID) of the 266 subjects (45%) did not have at least 1 blood sample collected for pharmacokinetic analysis. The remaining 146 subjects (55%) had at least 1 blood sample collected. At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

52

Study drug dosing errors were noted for 3 subjects. At the Baseline Visit, Primer Phase modules 17011 and 17001 were incorrectly dispensed to Subjects 4136 (placebo) and 4134 (ABT-594 150 µg BID), respectively. These subjects took incorrect study drug on Study Days 1 through 7. The subjects were also dispensed Treatment Phase modules at the same visit and these modules were dispensed correctly. Therefore, subjects 4136 and 4134 were each taking their correct randomized dose beginning on Study Day 8. One subject (4099) randomized to ABT-594 225 µg BID actually received ABT-594 300 µg BID (module 30157) on Study Days 21 through 37 (Appendix 16.2__5.1.1). In all efficacy and safety analyses, data for Subject 4099 were included in the ABT-594 225 µg BID treatment group.

11.0 Efficacy and Pharmacokinetic Evaluation

11.1 Data Sets Analyzed

The 266 randomized subjects who received at least 1 dose of study drug comprise the “all treated subjects” dataset and are included in the safety analyses. The primary efficacy dataset was the ITT dataset, which included all randomized subjects who took at least 1 dose of study drug and had at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale). Of the 266 all treated subjects, 251 were included in the ITT dataset (Tables 14.2__1.1 and 14.2__1.2).

In addition, efficacy analyses based on “evaluable” and “completers” data were performed. The 217 subjects who received at least 7 days of study drug and who had at least 1 pre-dose pain assessment and at least 1 post-Day 7 pain assessment for the diary-based Pain Rating Scale comprised the “evaluable” efficacy dataset (Tables 14.2__8.1 and 14.2__8.2). The 138 subjects who did not prematurely discontinue from the study for any reason were included in the completers data set. Efficacy ITT, evaluable, and completer exclusions are identified in the data listings.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

53

The treatment groups were similar with respect to the number and percentage of subjects contributed by each investigator in the ITT and evaluable datasets (Table 14.1__1.2).

A summary of subject accountability is presented in Table 11.1a.

Table 11.1a Disposition of Subjects by Dataset

	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
Number of Subjects Randomized	65	65	69	67
Subjects Included in the All Treated Subjects Dataset	65	65	69	67
Subjects Included in the Intent-to-Treat Dataset	62	61	66	62
Subjects Included in the Efficacy Evaluable Dataset	61	53	54	49
Subjects Included in the Completers Dataset	51	40	30	17

Cross Reference: Table 14.1__1.2 and Appendices 16.2__3.1, 16.2__3.2, and 16.2__3.3

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066050

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

54

11.2 Demographic and Other Baseline Characteristics

All demographic and other baseline characteristic results are for all treated subjects, unless otherwise specified. The location of demographic and other baseline characteristic data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Demographics	14.1__4.1	16.2__4.1
Medical History	14.1__5.1 14.1__5.2	16.2__4.2
Nicotine Consumption	14.1__4.1	16.2__4.3
Baseline Pain Assessments	14.1__6	16.2__6.2.1 16.2__6.2.2 16.2__6.3.1 16.2__6.3.2 16.2__6.4.1 16.2__6.4.2 16.2__6.4.3

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066051

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

55

11.2.1 Demographics

No statistically significant differences were observed among treatment groups for sex, race, age, height, or weight. The average age was 61.9 years (range = 20 - 86 years). Eighty-nine percent of the subjects were white. Subject demographic characteristics are presented in Table 11.2a.

Table 11.2a Demographic Characteristics (All Treated Subjects)

Demographic Characteristic	Treatment Group n (%)				p-value ^a
	Placebo (N=65)	ABT-594			
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)	
<u>Sex</u>					0.870
Female	27 (42%)	31 (48%)	33 (48%)	30 (45%)	
Male	38 (58%)	34 (52%)	36 (52%)	37 (55%)	
<u>Race^b</u>					0.751
White	57 (88%)	58 (89%)	64 (93%)	59 (88%)	
Black	7 (11%)	6 (9%)	3 (4%)	8 (12%)	
Asian	0	1 (2%)	1 (1%)	0	
Native American	0	0	1 (1%)	0	
Other	1 (2%)	0	0	0	
<u>Age (years)</u>					0.110
Mean (SD)	60.2 (11.43)	60.8 (10.78)	61.8 (11.80)	64.7 (11.10)	
Min-Max	20 - 80	36 - 85	24 - 84	31 - 86	
<u>Height (inches)^c</u>	(N=65)	(N=65)	(N=69)	(N=66)	0.300
Mean (SD)	68.4 (4.47)	67.5 (3.93)	67.1 (4.27)	67.3 (3.73)	
Min-Max	60 - 77	59 - 75	59 - 79	60 - 75	
<u>Weight (pounds)^c</u>					0.758
Mean (SD)	205.3 (36.44)	200.0 (40.03)	199.2 (34.57)	203.1 (34.94)	
Min-Max	127.9 - 275.0	113.0 - 276.0	112.0 - 258.0	134.5 - 277.8	
^a p-values are from extension of Fisher's exact test comparing treatment groups (sex, race), or a 1-way ANOVA model comparing treatment groups (age, height, and weight).					
^b Non-white races were combined for calculation of p-value. American Indian/Alaska Native was represented as Native American.					
^c At baseline.					

Cross Reference: Table 14.1__4.1 and Appendix 16.2__4.1

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066052

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

56

11.2.2 Other Baseline Characteristics

There were no statistically significant differences among treatment groups in the ITT analysis with respect to all pain assessment variables (including diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score) and other baseline characteristics including nicotine use. The baseline characteristics for the ITT dataset are presented in Table 11.2b.

Pain assessment scales are presented in Appendix 16.1.13.

Table 11.2b Other Baseline Characteristics (Intent-to-Treat Dataset)

Baseline Characteristic	Treatment Group				p-value ^a
	Placebo	ABT-594			
		150 µg BID	225 µg BID	300 µg BID	
Diary-Based Pain Scale ^b	(N=62)	(N=64)	(N=67)	(N=66)	0.847
Baseline Mean (SD)	6.5 (1.43)	6.6 (1.69)	6.7 (1.51)	6.7 (1.74)	
Site-Based Pain Scale ^b	(N=64)	(N=64)	(N=69)	(N=66)	0.608
Baseline Mean (SD)	6.5 (1.67)	6.7 (1.98)	6.7 (1.57)	6.9 (1.91)	
Neuropathic Pain Scale Total Score ^c	(N=64)	(N=65)	(N=69)	(N=64)	0.910
Baseline Mean (SD)	56.5 (17.47)	55.1 (17.47)	56.3 (15.18)	57.3 (19.81)	
Nicotine Used ^d	(N=65)	(N=65)	(N=69)	(N=67)	0.098
Former User	29 (45%)	24 (37%)	18 (26%)	25 (37%)	
Non-User	32 (49%)	31 (48%)	40 (58%)	38 (57%)	
Current User	4 (6%)	10 (15%)	11 (16%)	4 (6%)	

^a p-values are from extension of Fisher's exact test comparing treatment groups (nicotine use) or 1-way ANOVA model comparing treatment groups (pain scores).

^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

^c Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most.

^d Former users and non-users were combined for calculation of p-value.

^a p-values are from extension of Fisher's exact test comparing treatment groups (nicotine use) or 1-way ANOVA model comparing treatment groups (pain scores).

^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

^c Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most.

^d Former users and non-users were combined for calculation of p-value.

Cross Reference: Tables 14.1__4.1, 14.1__6 and Appendices 16.2__4.3, 16.2__6.2.1, 16.2__6.2.2, 16.2__6.3.1, 16.2__6.4.1, 16.2__6.4.2, and 16.2__6.4.3

A medical history was obtained for each subject who entered the study. Among currently symptomatic subjects, sporadic statistically significant differences were observed between each of the ABT-594 150 µg BID and 300 µg BID treatment groups and the placebo

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

57

treatment group for the proportions of subjects who had a specific condition/diagnosis (Table 14.1__5.1). Among currently asymptomatic subjects, no apparent differences were observed between treatment groups for the proportion of subjects with a specific condition/diagnosis (Table 14.1__5.2).

11.2.3 Concurrent Medication Use

The proportion of subjects using a concomitant medication during the study was similar among treatment groups. The number and proportion of subjects who took concomitant medications during the study and listing of subject numbers by therapeutic classifications are presented in Tables 14.1__7.1 and 14.1__7.2, respectively. Individual subject data listings for subjects who took previous and concomitant medications are presented in Appendix 16.2__7.3.

During the Baseline Pain Assessment Phase, no statistically significant difference was observed among treatment groups for the proportion of subjects who used protocol-allowed concomitant analgesic medication (Table 14.2__7.1).

11.3 Measurements of Treatment Compliance

The location of compliance and drug concentration data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Study Drug Administration	14.1__8	16.2__5.1.1 16.2__5.1.2
Plasma Assay	none	16.2__5.3.1 16.2__5.3.2

11.4 Efficacy Evaluations and Tabulations of Individual Subject Data

Each efficacy analysis compared the placebo treatment group versus each of the other ABT-594 treatment groups. Efficacy scale ranges are presented in Appendix 16.1.13.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

58

11.4.1 Efficacy Analyses

The location of efficacy data is presented below.

Assessment	Statistical Analyses Tables ^a	Individual Subject Listing Appendix
Diary-Based Pain Rating Scale	14.2__2.1.1.1	16.2__6.2.1
	14.2__2.1.1.2	
	14.2__2.1.2	
	14.2__2.1.3	
	14.2__2.1.4	
	14.2__2.2	
	14.2__2.3	
	14.2__2.4.1.1	
	14.2__2.4.1.2	
	14.2__2.4.2	
	14.2__2.4.3	
	14.2__2.4.4	
Site-Based Pain Rating Scale	14.2__3.1.1	16.2__6.2.2
	14.2__3.1.2	
	14.2__3.1.3	
	14.2__3.2	
	14.2__3.3	
	14.2__3.4	
Neuropathic Pain Scale	14.2__4.1.1	16.2__6.3.1
	14.2__4.1.2	16.2__6.3.2
	14.2__4.1.3	
	14.2__4.1.4	
	14.2__4.2	
	14.2__4.3	
	14.2__4.4	
Global Impression of Change	14.2__5.1	16.2__6.5
	14.2__5.2	
	14.2__5.3	
	14.2__5.4	
SF-36™ Health Status Survey	14.2__6	16.2__6.4.1
		16.2__6.4.2
		16.2__6.4.3
Concomitant Analgesic Medication Use	14.2__7.1	16.2__7.4
	14.2__7.2	
	14.2__7.3	

^a Statistical analyses tables for the ITT dataset.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066055

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

59

Analyses were performed on the ITT, evaluable, and study completers datasets using both the LOCF and OC methods; the ITT dataset was the protocol-defined primary dataset. Efficacy results are presented only for the ITT dataset. Efficacy results for the evaluable and study completers dataset were generally similar to those for the ITT dataset (Tables 14.2__8.1 through 14.2__13 and 14.2__14.1.1.1 through 14.2__18, respectively). Furthermore, results from analyses that used the OC method were generally similar to those that used the LOCF method, and differences are noted between the 2 methods.

11.4.1.1 Primary Efficacy Variable

Diary-Based Pain Rating Scale Scores at Final Evaluation

The mean improvement from baseline to final for the average diary-based Pain Rating Scale scores was statistically significantly greater for each of the ABT-594 treatment groups compared to placebo. A summary of the mean change from baseline to final for the average diary-based Pain Rating Scale scores is presented in Table 11.4a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

60

Table 11.4a Summary of the Analysis of Mean Change From Baseline^a to Final^b for the Average Diary-Based Pain Rating Scale^c Scores Using LOCF Method (Intent-to-Treat Dataset)

	Treatment Group			
	Placebo (N=58)	ABT-594		
		150 µg BID (N=56)	225 µg BID (N=58)	300 µg BID (N=53)
Baseline Visit Model-Based Mean (SE) ^d	6.5 (0.21)	6.6 (0.22)	6.7 (0.21)	6.7 (0.22)
Change to Final Model-Based Mean (SE) ^d	-1.1 (0.29)	-1.9 (0.30)*	-1.9 (0.29)*	-2.0 (0.30)*

SE = standard error.
 a Average of the last 7 pain scores prior to Day 1 of the study.
 b Average of the values from the last 7 days on study drug.
 c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
 d Least square means from 2-way ANOVA without interaction.
 * Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__2.1.1.1 and 14.2__2.1.1.2 and Appendix 16.2__6.2.1

A statistically significant linear dose response was observed for mean change from baseline to final for the average diary-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__2.3).

11.4.1.2 Secondary Efficacy Variables

Change From Baseline to Final

The mean improvement from baseline to final for the average site-based Pain Rating Scale scores was statistically significantly greater in each of the ABT-594 treatment groups compared to placebo.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

61

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. However, sporadic statistically significant differences were observed between placebo and 1 of the ABT-594 treatment groups for the mean change from baseline to final in the following items from the Neuropathic Pain Scale: intense, dull, and deep pain (Table 14.2__4.1.2).

In the analysis of the mean change from baseline to final in the SF-36™ Health Status Survey, a statistically significant difference was observed between the ABT-594 225 µg BID and placebo treatment groups in the physical component summary. Subjects in the ABT-594 225 µg BID treatment group showed a greater improvement from baseline compared to subjects in the placebo treatment group. Additionally, a statistically significant difference was observed between the ABT-594 300 µg BID and placebo treatment groups in the mental component summary. Subjects in the placebo treatment group showed an improvement from baseline, while subjects in the ABT-594 300 µg BID treatment group showed a deterioration from baseline. There were no other statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the SF-36™ Health Status Survey subscales.

A summary of the mean change from baseline to final for secondary efficacy variables is presented in Table 11.4b.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

62

Table 11.4b Change from Baseline to Final for Secondary Efficacy Variables^a Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Average Site-Based Pain Rating Scale ^b Scores	(N=57)	(N=47)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE) ^c	6.4 (0.25)	6.7 (0.27)	6.4 (0.30)	6.7 (0.34)
Change to Final				
Model-Based Mean (SE) ^c	-1.1 (0.36)	-2.7 (0.39)*	-2.1 (0.43)*	-2.8 (0.49)*
Neuropathic Pain Scaled Total Score	(N=57)	(N=48)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE) ^c	54.3 (2.32)	54.6 (2.55)	53.5 (2.82)	56.3 (3.16)
Change to Final				
Model-Based Mean (SE) ^c	-11.4 (3.04)	-16.1 (3.34)	-15.8 (3.69)	-19.7 (4.14)
SF-36 TM Health Status Survey Physical Component ^e	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE) ^c	35.0 (1.29)	32.7 (1.36)	32.7 (1.28)	34.3 (1.31)
Change to Final				
Model-Based Mean (SE) ^c	0.6 (0.97)	3.2 (1.02)	3.3 (0.96)*	0.7 (0.98)
SF-36 TM Health Status Survey Mental Component ^e	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE) ^c	47.9 (1.50)	50.5 (1.59)	50.6 (1.49)	49.6 (1.52)
Change to Final				
Model-Based Mean (SE) ^c	1.7 (1.29)	-0.9 (1.35)	-1.3 (1.27)	-1.9 (1.30)*

NOTE: Due to the number of subjects who dropped out or failed to complete certain efficacy assessments, the number of subjects included in each of the secondary efficacy analyses was smaller than that of the primary analyses.

^a Pain assessment scales are presented in Appendix 16.1.13.

^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

^c Values represent model-based means (SE) which are least square means from 2-way ANOVA without interaction.

^d Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most for each of the 10 items.

^e Results based on transformed scores as calculated using SF-36TM health survey manual and interpretation guide.

* Statistically significant difference versus placebo treatment group (p≤0.05).

Cross Reference: Tables 14.2__3.1.1, 14.2__4.1.1, and 14.2__6 and Appendices 16.2__6.2.2, 16.2__6.3.1, 16.2__6.4.1, and 16.2__6.4.2

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066059

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

63

Global Impression of Change

No statistically significant differences were observed between the placebo and each of the ABT-594 treatment groups in the mean overall change from baseline in the subject and clinician global impression of change. However, each of the ABT-594 treatment groups was numerically better than placebo. A summary of the mean change from baseline to final for subject and clinician global impression of change is presented in Table 11.4c.

Table 11.4c Change from Baseline to Final for Subject and Clinician Global Impression of Change^a Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Subject Global Impression of Change ^b	(N=61)	(N=59)	(N=61)	(N=59)
Univariate Mean Change (SE) ^c	0.8 (0.18)	0.8 (0.21)	1.3 (0.21)	1.1 (0.19)
Clinician Global Impression of Change ^b	(N=61)	(N=59)	(N=60)	(N=59)
Univariate Mean Change (SE) ^c	0.7 (0.17)	0.8 (0.21)	1.2 (0.18)	1.1 (0.18)

^a Pain assessment scales are presented in Appendix 16.1.13.
^b Overall change defined as follows: 3 = much improved, 2 = moderately improved, 1 = minimally improved, 0 = no change, -1 = minimally worse, -2 = moderately worse, -3 = much worse.
^c Values represent univariate means (SE) for the Cochran-Mantel-Haenszel test.

Cross Reference: Table 14.2__5.3 and Appendix 16.2__6.5

In the distribution analyses of subject and clinician global impression of change (much, moderately, or minimally improved, no change, or much, moderately, or minimally worse) statistically significant differences from placebo were observed for the ABT-594 225 µg BID treatment group (Table 14.2__5.1). When responses were further categorized as improved (including much, moderate, or minimal), no change,

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

64

or worsened (including much, moderate, or minimal), there was a statistically significant difference between the ABT-594 225 µg BID and placebo treatment groups for clinician global impression of change. Based on the clinician's assessment, a greater proportion of subjects in the ABT-594 225 µg BID treatment group were improved (63%) compared to subjects in the placebo treatment group (42%; Table 14.2__5.2).

Dose Response

A statistically significant linear dose response was observed for mean change from baseline to final for the average site-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__3.3). No statistically significant linear dose response was observed for mean change from baseline to final for the Neuropathic Pain Scale Total Score, regardless of whether the model included or excluded the placebo treatment group (Table 14.2__4.3).

Change From Baseline to Each Week - Diary-Based Pain Rating Scale

Improvements from baseline were seen in diary-based Pain Rating Scale scores at each week for all treatment groups. In the LOCF analyses, the ABT-594 150 µg BID treatment group had statistically significantly greater mean improvements from baseline to Weeks 5, 6, and 7 for the average diary-based Pain Rating Scale scores when compared to placebo. No statistically significant differences were observed between the ABT-594 225 µg BID and placebo treatment groups at any time point. The mean improvements from baseline to Weeks 3, 4, 5, and 7 for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo. Results of OC analyses were generally similar to those of LOCF analyses, with a more consistent treatment effect observed in the OC analyses. A summary of the mean change from baseline to each week for the average diary-based Pain Rating Scale scores is presented in Table 11.4d.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

65

Table 11.4d Summary of the Analysis of Mean Change From Baseline^a to Each Week for the Average Diary-Based Pain Rating Scale^b Scores Using LOCF and OC Methods (Intent-to-Treat Dataset)

Visit	Treatment Group							
	Placebo		ABT-594					
			150 µg BID		225 µg BID		300 µg BID	
	LOCF (N=58)	OC (N=c)	LOCF (N=56)	OC (N=c)	LOCF (N=58)	OC (N=c)	LOCF (N=53)	OC (N=c)
Baseline Mean ^d	6.5	6.5 ^e	6.6	6.6	6.7	6.7	6.7	6.7
Week 1 ^d	-0.6 ^f	-0.6	-0.8	-0.8	-0.8	-0.8	-0.7	-0.7
Week 2 ^d	-1.0 ^f	-1.0	-1.1	-1.1	-1.2	-1.3	-1.4	-1.8*
Week 3 ^d	-1.0	-0.9	-1.2	-1.4	-1.5	-2.0*	-1.7*	-2.4*
Week 4 ^d	-1.1	-1.1	-1.6	-1.9*	-1.5	-2.3*	-1.9*	-2.4*
Week 5 ^d	-1.0	-1.0	-1.8*	-2.3*	-1.7	-2.5*	-1.9*	-2.9*
Week 6 ^d	-1.1	-1.1	-1.9*	-2.4*	-1.7	-2.6*	-1.8	-2.8*
Week 7 ^d	-1.1	-1.0	-1.9*	-2.4*	-1.8	-2.6*	-1.9*	-3.1*

LOCF = last observation carried forward; OC = observed cases.
Note: All values represent model-based means.

^a Average of the last 7 pain scores prior to Day 1 of the study.
^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
^c No's for observed cases analyses:

	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Week 1	57	56	58	53
Week 2	56	49	44	38
Week 3	56	47	37	27
Week 4	52	44	34	23
Week 5	50	39	33	20
Week 6	50	39	30	17
Week 7	49	38	29	17

^d Least square means from 2-way ANOVA without interaction.
^e N = 58 at baseline.
^f N = 57 at Weeks 1 and 2.
* Statistically significant difference versus placebo treatment group (p≤0.05).

Cross Reference: Tables 14.2__2.1.3 and 14.2__2.4.3 and Appendix 16.2__6.2.1

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066062

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

66

Change From Baseline to Each Visit - Diary-Based Pain Rating Scale

Each treatment group showed improvement from baseline to the 7-day average prior to each visit in diary-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits III and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 µg BID and 225 µg BID treatment groups compared to placebo. Furthermore, the mean changes from baseline to Treatment Visits II, III, and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo (Table 14.2__2.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__2.4.2).

Change From Baseline to Each Visit - Site-Based Pain Rating Scale

Each treatment group showed improvement from baseline to each visit in site-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits II, III, and IV for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 µg BID treatment group compared to placebo. The mean change from baseline to Treatment Visit IV for the average site-based Pain Rating Scale score was statistically significantly greater in the ABT-594 225 µg BID treatment group compared to placebo. The mean changes from baseline to each Treatment Visit for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo (Table 14.2__3.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__3.4).

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

67

11.4.1.3 Other Efficacy Variables

Proportion of Responders

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to the final evaluation, was analyzed for the following efficacy variables: average diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either the diary- or site-based average Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group. A summary of the proportion of subjects with a positive response to study drug as measured by average diary- and site-based Pain Rating Scale scores is presented in Table 11.4e.

Table 11.4e Proportion of Subjects Responding^a to Treatment as Measured by Diary- and Site-Based Pain Rating Scale Scores^b Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Average Diary-Based Pain Rating Scale ^c Scores	(N=58) 12%	(N=56) 27%*	(N=58) 26%	(N=53) 26%*
Average Site-Based Pain Rating Scale ^c Scores	(N=57) 14%	(N=47) 40%*	(N=40) 35%*	(N=29) 48%*

^a Defined as a 50% or greater improvement from baseline to the final evaluation.
^b Pain assessment scales are presented in Appendix 16.1.13.
^c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
 * Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2__2.1.4 and 14.2__3.1.3 and Appendices 16.2__6.2.1 and 16.2__6.2.2

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

68

Concomitant Analgesic Medication Use

No statistically significant differences were observed among the treatment groups for the proportion of subjects using any analgesic medication or within 24 hours of analgesic medication at each visit during the Treatment Phase and over the entire Treatment Phase (Tables 14.2__7.1 and 14.2__7.2). There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the number of times analgesic medication was used (Table 14.2__7.3).

11.4.2 Statistical and Analytical Issues

11.4.2.1 Adjustments for Covariates

Adjustments for covariates, including sex, race, age, and weight, were not performed in the efficacy analyses.

11.4.2.2 Handling of Dropouts or Missing Data

Two sets of efficacy analyses, corresponding to the handling of missing data, were performed. The LOCF analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had a value for each specified evaluation. This technique was intended to reduce bias caused by subjects who prematurely discontinued due to lack of efficacy. The OC method did not estimate missing evaluations and a subject who did not have a pain evaluation on a scheduled visit was excluded from the OC analysis for that visit. Results obtained with the OC method were generally consistent with those obtained with the LOCF method.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

69

11.4.2.4 Multicenter Studies

This was a multicenter study. The treatment-by-center interaction was not statistically significant at an $\alpha=0.10$ in the analysis of change from baseline to the final evaluation for the diary-based Pain Rating Scale scores (Table 14.2__2.2), indicating homogeneity of treatment effects across centers for the primary endpoint. Therefore, the treatment-by-center interaction term was not used in the primary or secondary analyses. Additionally, since the treatment-by-center interaction term was not used in the primary analysis, data from study centers with less than 1 subject per treatment group in the ITT dataset, were not combined for the analyses.

11.4.2.5 Multiple Comparisons/Multiplicity

No statistical adjustments were made for multiple comparisons.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

Subjects who received less than 7 days of study drug or who had no baseline or post Day 7 pain assessment for the diary-based Pain Rating Scale were identified prior to breaking the blind and were excluded from the evaluable dataset. Results for ITT and evaluable datasets were similar.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

The study was not designed to assess equivalence to an active control.

11.4.2.8 Examination of Subgroups

Subgroup analyses for potentially influential factors were not performed.

Part 5

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

70

11.4.3 Tabulation of Individual Response Data

There were no tabulations of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.4 Drug Dose, Drug Concentration, and Relationship to Response

Blood samples for ABT-594 plasma assay were to be collected for all subjects at Treatment Visits I and IV. For those subjects participating in the pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), additional blood samples were collected at Treatment Visits I and IV. Plasma concentrations of ABT-594 are listed for each subject in Appendix 16.2__5.3.1.

A complete discussion of the pharmacokinetic variables analyzed will be presented in a separate Clinical Pharmacokinetic Report.

11.4.5 Drug-Drug and Drug-Disease Interactions

Analyses which examined drug-drug and drug-disease interactions were not performed.

11.4.6 By-Subject Displays

There were no by-subject displays of individual response to study drug except as provided in the data listings (Appendix 16.2).

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

71

11.4.7 Efficacy Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

11.5 Pharmacokinetic Variables

Complete pharmacokinetic results will be presented in a separate Clinical Pharmacokinetic Report.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

72

12.0 Safety Evaluation

All 266 randomized subjects who were treated with study drug (65 placebo, 65 ABT-594 150 µg, 69 ABT-594 225 µg, and 67 ABT-594 300 µg BID) were evaluated for safety. Adverse events, clinical laboratory data, vital signs (including weight), and 12-lead ECG data were used to evaluate safety.

12.1 Extent of Exposure

The mean duration of treatment was statistically significantly different among treatment groups. The placebo treatment group received study drug for a mean 44.3 days, as compared to 35.9, 28.6, and 22.7 days for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups, respectively. A summary of the extent of exposure to study drug is presented in Table 12.1a.

Table 12.1a Extent of Exposure

Duration of Treatment (Days)	Treatment Group n (%)			
	Placebo (N=65)	ABT-594		
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
<7	1 (2%)	8 (12%)	14 (20%)	12 (18%)
7 - 13	2 (3%)	5 (8%)	14 (20%)	19 (28%)
14 - 20	4 (6%)	4 (6%)	4 (6%)	6 (9%)
21 - 27	5 (8%)	6 (9%)	3 (4%)	8 (12%)
28 - 34	0	2 (3%)	0	3 (4%)
35 - 41	1 (2%)	0	4 (6%)	2 (3%)
42 - 48	3 (5%)	5 (8%)	3 (4%)	1 (1%)
≥49	49 (75%)	35 (54%)	27 (39%)	16 (24%)
Mean (SD)*	44.3 (13.5)	35.9 (19.1)	28.6 (20.5)	22.7 (18.0)

Note: Percentages may not sum to 100 due to rounding.
 SD = standard deviation.
 * Statistically significant difference among treatment groups ($p \leq 0.05$).

Cross Reference: Table 14.1__8 and Appendix 16.2__5.1.1

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066069

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

73

12.2 Adverse Events

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Adverse Events		16.2__7.1.1
All Treatment-Emergent	14.3.1__1.1	
by Severity	14.3.1__1.2.1	
	14.3.1__1.2.2	
by Relationship to Study Drug	14.3.1__1.3.1	
	14.3.1__1.3.2	
Incidence Across Time	14.3.1__2.1	
Prevalence Across Time	14.3.1__2.2	
Identification of Subjects	14.3.1__3.1	
Medical Terms and Descriptions Associated with Each COSTART Term	14.3.1__3.2	

12.2.1 Brief Summary of Adverse Events

Among all treated subjects, 66% of subjects who received placebo and 83%, 90%, and 91% of subjects who received ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

74

300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, vomiting, dizziness, abnormal dreams, and headache.

12.2.2 Display of Adverse Events

A summary of the treatment-emergent adverse events occurring in $\geq 10\%$ of subjects in any ABT-594 treatment group is presented by the investigator's assessment of relationship to study drug in Table 12.2a.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

75

Table 12.2a Summary of Most Frequently Reported Treatment-Emergent Adverse Events By Relationship to Study Drug

COSTART Term	Treatment Group n (%)																											
	Placebo (N=65)							ABT-594																				
	150 µg BID (N=65)							225 µg BID (N=69)							300 µg BID (N=67)													
	Relationship ^b				Total			Relationship ^b				Total			Relationship ^b				Total									
NR	PN	PO	PR	n	%		NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%	NR	PN	PO	PR	n	%				
Any Event	0	0	2	5	43	66%		0	1	5	16	54	83%*		1	0	5	24	62	90%*		1	0	3	27	61	91%*	
Nausea	1	1	0	1	3	5%		0	1	2	8	11	17%*		0	3	3	18	30	43%*		0	0	3	17	31	46%*	
Dizziness	0	0	1	1	2	3%		0	0	1	9	10	15%*		1	0	3	13	17	24	35%*		1	1	1	11	20	30%*
Vomiting	0	0	0	0	0	0%		0	0	2	12	14	22%*		0	0	1	14	15	22%*		0	0	2	10	12	18%*	
Abnormal Dreams	2	2	3	1	8	12%		3	3	3	4	13	20%		2	2	0	6	10	14%		1	0	1	11	13	19%	
Headache	0	0	0	1	1	2%		0	0	3	1	4	6%		0	0	3	8	11	16%*		0	1	2	11	14	21%*	
Asthenia	0	0	0	2	2	3%		1	2	2	2	7	11%		2	0	2	4	8	12%		1	1	0	2	4	6%	
Diarrhea	0	0	2	0	2	3%		0	0	3	2	5	8%		0	0	0	8	8	12%		0	0	1	4	5	7%	
Dyspepsia	0	1	2	0	3	5%		0	0	1	0	1	2%		1	1	2	5	9	13%		0	0	2	5	7	10%	
Insomnia																												

NR = not related; PN = probably not related; PO = possibly related; PR = probably related.

^a Adverse events occurring in ≥10% of subjects in any ABT-594 treatment group.

^b As assessed by the investigator.

Statistically significant difference versus the placebo treatment group (n<0.05)

NR = not related; PN = probably not related; PO = possibly related; PR = probably related.

^a Adverse events occurring in ≥10% of subjects in any ABT-594 treatment group.

^b As assessed by the investigator.

* Statistically significant difference versus the placebo treatment group (p≤0.05).

Cross Reference: Tables 14.3.1.1.1, 14.3.1.1.3.1 and 14.3.1.1.3.2 and Appendix 16.2.7.1.1

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

76

Most adverse events in all treatment groups were mild or moderate in severity and were considered by the investigator to be possibly or probably related to study drug (Tables 14.3.1__1.2.1, 14.3.1__1.2.2, 14.3.1__1.3.1, and 14.3.1__1.3.2).

12.2.3 Analysis of Adverse Events

The overall incidence of treatment-emergent adverse events was statistically significantly higher for subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (83%, 90%, and 91%, respectively) than for subjects in the placebo treatment group (66%). Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). No other statistically significant treatment differences were observed for any specific treatment-emergent adverse event (Table 14.3.1__1.1).

Five percent (3/65) of placebo-treated subjects, 11% (7/65) of ABT-594 150 µg-treated subjects, 12% (8/69) of ABT-594 225 µg-treated subjects, and 12% (8/67) of ABT-594 300 µg BID-treated subjects experienced at least 1 severe adverse event, most of which were considered probably related to study drug by the investigator. The remaining adverse events were mild or moderate in severity. A summary of the severity of treatment-emergent adverse events grouped by body system and COSTART term is presented in Tables 14.3.1__1.2.1 and 14.3.1__1.2.2.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

77

12.2.4 Listing of Adverse Events by Subject

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Treatment-Emergent Adverse Events Grouped by Body System, COSTART Term, Medical Term, and Description With Subject Number Identification (All Treated Subjects)	14.3.1__3.1	16.2__7.1.1
Adverse Event Medical Terms and Descriptions	14.3.1__3.2	

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The location of deaths, other serious adverse events, and other significant adverse event data is presented below.

Assessment	Statistical Analyses Tables	Narrative Section	Individual Subject Listing Appendix
Deaths	14.3.2__1.1	14.3.3	16.2__7.2
Serious Adverse Events	14.3.2__1.2	14.3.3	16.2__7.1.2
Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued	14.3.2__2	14.3.3	16.2__7.1.1
Number and Percentage of Subjects With Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued Grouped by Body System and COSTART Term	14.3.2__3		16.2__7.1.1

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066074

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

78

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug.

A listing of subjects who died during the course of the study is presented in Appendix 16.2__7.2.

12.3.1.2 Other Serious Adverse Events

In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported a serious adverse event during the study (Table 14.3.2__1.2). One of these subjects reported an event (palpitation reported in an ABT-594 300 µg BID-treated subject) considered probably related to study drug. The event was a single occurrence and resolved within 90 minutes. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as “status post fall down stairs”]) with onset >30 days after the last dose of study drug.

Eight subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each of these subjects had multiple risk factors for cardiovascular disease. Subjects reporting serious adverse events (including death) during the study are presented in Table 12.3a.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

79

Table 12.3a Subjects Reporting Serious Adverse Events During the Study

Treatment Group	Investigator/ Subject	Age (yrs)/ Sex	Day of Onset ^a	Day of Resolution ^a	COSTART Term - Reason Serious ^b	Relationship to Study Drug
Placebo	DeBold/4053	52/F	52 (2)	53 (3)	Gastroenteritis - HO	Not related
			52 (2)	53 (3)	Dehydration - HO	Not related
			52 (2)	53 (3)	Ketosis - HO	Not related
Placebo	Singer/4401	53/M	34	42 (1)	Angina Pectoris ^c - HO	Not related
			49 (9)	unknown	Atrial Fibrillation - HO	Not related
	Weinstein/4027	65/F	9 (1)	12 (4)	Cerebrovascular Accident ^c - HO	Probably not
ABT-594 150 µg BID	Baumel/4149	71/M	65 (15)	66 (16)	Angina Pectoris - HO	Not related
			65 (15)	66 (16)	Myocardial Infarct - HO	Not related
	Fried/4083	66/F	15 (1)	17 (3) ^d	Syncope ^c - HO	Not related
			15 (1)	22 (3) ^d	Atrial Fibrillation ^c - HO	Not related
	Kipnes/4070	48/F	10	12	Pain ^c - HO	Not related
	Singer/4412	57/M	36	50	Peripheral Vascular Disorder - HO	Not related
ABT-594 225 µg BID	Storey/4100 ^e	56/F	79 (58) ^f	79 (58)	Suicide Attempt - DEA	Not related
	Kluge/4133	66/M	6	9	Gastrointestinal Disorder ^c - HO	Not related
	Shaibani/4451	60/F	18	18	Dyspnea ^c - HO	Probably not
ABT-594 300 µg BID			18	20 (2)	Angina Pectoris ^c - HO	Probably not
	Drucker/4002	70/M	4	4	Palpitation ^c - HO	Probably
	Holmlund/4193 ^e	55/M	40 (32) ^f	64 (56)	Accidental Injury ^g - HO	Not related
	Holmlund/4197	62/F	5	6 (1)	Angina Pectoris ^c - HO	Not related
	Weinstein/4031	80/M	43 (7)	80 (44) ^d	Cellulitis ^c - HO	Not related
<p>M = male, F = female.</p> <p>^a Number in parentheses represents the number of days after the last dose of study drug.</p> <p>^b HO=hospitalization; DEA=death.</p> <p>^c Adverse event leading to premature discontinuation.</p> <p>^d Adverse event was ongoing as of this day.</p> <p>^e Subject prematurely discontinued due to another adverse event.</p> <p>^f Adverse event onset >30 days after the last dose of study drug.</p> <p>^g Described as status post fall down stairs.</p>						

Cross Reference: Table 14.3.2__1.2 and Appendices 16.2.__7.1.1 and 16.2__7.1.2

A listing of all subjects who experienced serious adverse events during the study is presented by treatment group and subject number in Table 14.3.2__1.2.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066076

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

80

12.3.1.3 Other Significant Adverse Events

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

A summary of adverse events leading to premature discontinuation of study drug is presented by treatment group in Table 12.3b.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

81

Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects)

COSTART Term	Treatment Group n (%)			
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Any Event ^a	6 (9%)	18 (28%)*	32 (46%)*	44 (66%)*
Nausea	1 (2%)	8 (12%)*	15 (22%)*	20 (30%)*
Dizziness	0	4 (6%)	11 (16%)*	13 (19%)*
Vomiting	0	4 (6%)	10 (14%)*	12 (18%)*
Abnormal Dreams	0	3 (5%)	6 (9%)*	7 (10%)*
Headache	0	1 (2%)	3 (4%)	8 (12%)*
Insomnia	0	1 (2%)	5 (7%)	4 (6%)
Asthenia	0	0	3 (4%)	6 (9%)*
Dyspepsia	0	2 (3%)	4 (6%)	3 (4%)
Diarrhea	0	0	4 (6%)	2 (3%)
Pain	0	1 (2%)	1 (1%)	4 (6%)
Sweating	0	1 (2%)	2 (3%)	2 (3%)
Chills	0	0	2 (3%)	2 (3%)
Flatulence	1 (2%)	0	1 (1%)	2 (3%)
Hypertension	0	0	2 (3%)	2 (3%)
Nervousness	0	0	3 (4%)	1 (1%)
Abdominal Pain	0	0	1 (1%)	2 (3%)
Angina Pectoris	1 (2%)	0	1 (1%)	1 (1%)
Chest Pain	0	0	1 (1%)	2 (3%)
Dyspnea	0	0	1 (1%)	2 (3%)
Palpitation	0	0	1 (1%)	2 (3%)
Taste Perversion	0	2 (3%)	0	1 (1%)
Abnormal Gait	0	0	2 (3%)	0
Accidental Injury	1 (2%)	0	0	1 (1%)
Amblyopia	0	1 (2%)	1 (1%)	0
Anorexia	0	0	1 (1%)	1 (1%)
Confusion	0	0	1 (1%)	1 (1%)
Hallucinations	0	0	2 (3%)	0
Malaise	0	0	1 (1%)	1 (1%)
Paresthesia	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	1 (1%)
Thinking Abnormal	0	0	0	2 (3%)
Abdomen Enlarged	0	0	0	1 (1%)
Abnormal Vision	0	0	0	1 (1%)
Alopecia	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Arthralgia	0	0	1 (1%)	0
Ataxia	0	0	1 (1%)	0
Atrial Fibrillation	0	1 (2%)	0	0
Back Pain	0	0	0	1 (1%)

^a Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066078

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

82

Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects; continued)

COSTART Term	Treatment Group n (%)			
	ABT-594			
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Cellulitis	0	0	0	1 (1%)
Cerebrovascular Accident	1 (2%)	0	0	0
Depersonalization	1 (2%)	0	0	0
Depression	0	0	0	1 (1%)
Dry Mouth	0	0	0	1 (1%)
Emotional Lability	0	0	1 (1%)	0
Eructation	0	0	0	1 (1%)
Eye Disorder	0	0	1 (1%)	0
Flu Syndrome	0	0	0	1 (1%)
Gastroenteritis	1 (2%)	0	0	0
Gastrointestinal Disorder	0	0	1 (1%)	0
Glossitis	0	1 (2%)	0	0
Hyperglycemia	0	0	0	1 (1%)
Infection	1 (2%)	0	0	0
Leg Cramps	0	0	0	1 (1%)
Myalgia	0	0	1 (1%)	0
Rash	0	0	0	1 (1%)
Rectal Hemorrhage	0	0	0	1 (1%)
Somnolence	0	1 (2%)	0	0
Stupor	0	0	0	1 (1%)
Syncope	0	1 (2%)	0	0
Tremor	0	0	1 (1%)	0
Vasodilatation	0	0	0	1 (1%)
^a Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.				
* Statistically significant difference versus the placebo treatment group (p≤0.05).				

Cross Reference: Table 14.3.2__3 and Appendix 16.2__7.1.1

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066079

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

83

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Narratives for subjects who died, reported a serious adverse event, or prematurely discontinued from the study at least in part to an adverse event are presented in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase (Table 14.3.2__1.1). Subject 4100 died on Day 79 due to a suicide attempt (COSTART term: suicide attempt) that the investigator considered to be unrelated to study drug.

Thirteen subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported 1 or more serious adverse events other than death. However, only 1 of these subjects (ABT-594 300 µg BID) reported an event considered to be probably related to study drug. This subject had a single episode of palpitation (COSTART term: palpitation) on Day 4 that resolved without further incident within 90 minutes. The remaining events were all considered to be not related or probably not related to study drug. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The overall incidence of subjects prematurely discontinuing due to adverse events was statistically significantly higher for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (28%, 46%, and 66%, respectively) than for the placebo treatment group (9%). Statistically significantly higher proportions of subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups prematurely discontinued study drug due to nausea (12%, 22%, and 30%, respectively) compared to subjects in the placebo treatment group (2%). Statistically significantly higher proportions of subjects in the ABT-594 225 µg and 300 µg BID treatment groups prematurely discontinued study drug

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

84

due to dizziness (16% and 19%, respectively), vomiting (14% and 18%, respectively), and abnormal dreams (9% and 10%, respectively) compared to subjects in the placebo treatment group (0% each). A statistically significantly higher proportion of subjects in the ABT-594 300 µg BID treatment group prematurely discontinued study drug due to headache (12%) and asthenia (9%) compared to subjects in the placebo treatment group (0% and 0%, respectively).

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

The location of clinical laboratory data is presented below.

Laboratory Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing ^a Appendix
Hematology	14.3.4__1.1	14.3.4__3.1	16.2__8.2.1
	14.3.4__2.1	14.3.4__4.1	16.2__8.2.2
			16.2__8.2.3
			16.2__8.2.4
			16.2__8.2.5
Blood Chemistry	14.3.4__1.2	14.3.4__3.2	16.2__8.3.1
	14.3.4__2.2	14.3.4__4.2	16.2__8.3.2
			16.2__8.3.3
			16.2__8.3.4
			16.2__8.3.5
Urinalysis			16.2__8.3.6
	14.3.4__1.3	14.3.4__3.3	16.2__8.4.1
	14.3.4__2.3	14.3.4__4.3	16.2__8.4.2
			16.2__8.4.3
			16.2__8.4.4
			16.2__8.4.5

^a Baseline determinations are also presented in Appendix 16.2__4.

Laboratory normal reference ranges are presented in Appendix 16.2__8.1. Criteria for potentially clinically significant laboratory values (i.e., very high or very low values) are presented in Table 14.3.4__1.0.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066081

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

85

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Hematology

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for hematology parameters is presented in Table 12.4a.

Part 6

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

86

Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters

Hematology Parameter (units)	Treatment Group			
	Placebo (N=62) ^a	ABT-594		
		150 µg BID (N=61) ^a	225 µg BID (N=66)	300 µg BID (N=62)
Hemoglobin (g/dL)				
Baseline Mean	14.10	13.80	13.81	14.02
Mean Change to Minimum	-0.46	-0.30	-0.21*	-0.09*
Hematocrit (%)				
Baseline Mean	40.95	40.39	40.11	40.82
Mean Change to Minimum	-1.06	-1.16	-0.79	-0.26*
Mean Change to Maximum	1.60	0.87	0.73*	0.90
RBC Count (x 10 ¹² /L)				
Baseline Mean	4.66	4.61	4.58	4.70
Mean Change to Minimum	-0.13	-0.11	-0.05*	-0.05*
MCV (fL)				
Baseline Mean	88.24	87.79	87.65	87.26
Mean Change to Maximum	2.00	1.26	0.68*	1.24
MCH (pg)				
Baseline Mean	30.52	30.07	30.21	30.00
Mean Change to Minimum	-0.73	-0.30*	-0.33*	-0.27*
Mean Change to Final	-0.29	0.16*	-0.08	0.00
MCHC (g/dL)				
Baseline Mean	34.50	34.30	34.45	34.47
Mean Change to Minimum	-1.08	-0.46*	-0.47*	-0.52*
Platelet Count (x 10 ⁹ /L)				
Baseline Mean	246.70	250.27	253.70	241.32
Mean Change to Minimum	-10.98	-13.27	-7.82	4.05*
Mean Change to Maximum	29.33	14.15*	10.89*	26.84
WBC Count (x 10 ⁹ /L)				
Baseline Mean	8.01	7.60	7.36	6.95
Mean Change to Minimum	-0.51	-0.50	-0.03*	0.02*
Neutrophils (%)				
Baseline Mean	61.01	62.82	61.86	60.62
Mean Change to Minimum	-2.25	-2.39	-0.60	0.09*
Lymphocytes (%)				
Baseline Mean	30.04	28.78	29.70	30.53
Mean Change to Maximum	2.08	2.17	0.63	0.02*
Eosinophils (%)				
Baseline Mean	2.90	2.32	2.38	2.53
Mean Change to Minimum	-0.82	-0.50	-0.34*	-0.60
Mean Change to Maximum	0.41	0.32	0.29	-0.05*
* Statistically significant difference versus the placebo treatment group (p≤0.05).				
^a N=60 for Platelet Count only				

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066083

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

87

Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters (continued)

Hematology Parameter (units)	Treatment Group			
	Placebo (N=60)	ABT-594		
		150 µg BID (N=59)	225 µg BID (N=65)	300 µg BID (N=61)
Prothrombin Time (sec)				
Baseline Mean	12.30	12.33	12.20	12.79
Mean Change to Maximum	0.39	0.15	0.08*	0.25
Activated Partial Thromboplastin Time (sec)				
Baseline Mean	24.32	24.69	25.11	25.53
Mean Change to Maximum	1.60	0.72	0.57*	0.27*
Mean Change to Final	0.56	-0.13	-0.24	-0.53*
* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).				

Cross Reference: Table 14.3.4__1.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Blood Chemistry

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for blood chemistry parameters is presented in Table 12.4b.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

88

Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters

Blood Chemistry Parameter (units)	Treatment Group			
	Placebo (N=62)	ABT-594		
		150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Glucose (mg/dL)				
Baseline Mean	175.68	192.13	169.09	183.90
Mean Change to Maximum	57.79	44.36	39.39	17.94*
Total Protein (g/dL)				
Baseline Mean	7.25	7.24	7.31	7.26
Mean Change to Maximum	0.19	0.14	0.03*	0.13
Mean Change to Final	0.03	-0.06	-0.13*	0.00
Total Bilirubin (mg/dL)				
Baseline Mean	0.40	0.43	0.38	0.36
Mean Change to Minimum	-0.05	-0.07	-0.04	-0.00*
Alkaline Phosphatase (IU/L)				
Baseline Mean	75.94	78.74	81.88	74.35
Mean Change to Maximum	4.27	1.43	-0.14*	1.95
SGOT/AST (IU/L)				
Baseline Mean	22.35	21.87	23.70	22.81
Mean Change to Maximum	2.76	1.56	-1.32*	0.84
SGPT/ALT (IU/L)				
Baseline Mean	23.08	24.11	24.65	26.42
Mean Change to Maximum	3.69	0.79	-1.44*	0.08
Sodium (mEq/L)				
Baseline Mean	141.18	139.82	140.85	140.16
Mean Change to Minimum	-2.77	-1.59	-1.92	-0.87*
Potassium (mEq/L)				
Baseline Mean	4.55	4.41	4.53	4.38
Mean Change to Minimum	-0.32	-0.15*	-0.19	-0.15*
Chloride (mEq/L)				
Baseline Mean	104.37	102.56	103.32	102.23
Mean Change to Minimum	-3.00	-1.15*	-1.95	-1.34*
Mean Change to Final	-0.71	0.80*	-1.00	0.29
Bicarbonate (mEq/L)				
Baseline Mean	26.42	26.72	27.10	27.57
Mean Change to Maximum	1.26	0.33*	0.71	0.61
Calcium (mg/dL)				
Baseline Mean	9.51	9.46	9.57	9.51
Mean Change to Minimum	-0.33	-0.17*	-0.21	-0.07*
Inorganic Phosphorus (mg/dL)				
Baseline Mean	3.64	3.71	3.72	3.56
Mean Change to Minimum	-0.42	-0.27	-0.11*	-0.11*
* Statistically significant difference versus the placebo treatment group (p<0.05).				

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066085

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

89

Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters (continued)

Blood Chemistry Parameter (units)	Treatment Group			
	Placebo (N=62)	ABT-594		
		150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Cholesterol (mg/dL)				
Baseline Mean	190.44	199.54	204.95	203.79
Mean Change to Maximum	12.71	4.44*	-1.05*	0.21*
Mean Change to Final	1.27	-3.66	-8.55*	-5.53
Triglycerides (mg/dL)				
Baseline Mean	239.31	274.03	277.55	300.03
Mean Change to Maximum	80.69	42.26	28.77*	-7.34*
Mean Change to Final	39.32	-9.11*	-3.59	-36.23*
* Statistically significant difference versus the placebo treatment group (p≤0.05).				

Cross Reference: Table 14.3.4__1.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Urinalysis

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for urinalysis is presented in Table 12.4c.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

90

Table 12.4c Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Urinalysis Parameters

Urinalysis Parameter (units)	Treatment Group			
	Placebo (N=61)	ABT-594		
		150 µg BID (N=58)	225 µg BID (N=65)	300 µg BID (N=62)
Urine pH				
Baseline Mean	5.75	5.59	5.51	5.68
Mean Change to Minimum	-0.67	-0.36*	-0.26*	-0.19*
Mean Change to Final	-0.34	-0.12	-0.09	0.00*
Specific Gravity				
Baseline Mean	1.02	1.02	1.02	1.02
Mean Change to Minimum	-0.004	-0.003	-0.002	-0.001*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

12.4.2.2 Individual Subject Changes

The percentage of subjects with shifts in laboratory parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.4__2.1 for hematology variables, Table 14.3.4__2.2 for blood chemistry variables, and Table 14.3.4__2.3 for urinalysis variables. The majority of subjects had clinical laboratory values within normal range at the Baseline and Final Visits.

12.4.2.3 Individual Clinically Significant Abnormalities

Hematology Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant hematology values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.1. The percentages of subjects who had hematology values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

91

hematology values that met the potentially clinically significant criteria are presented in Table 12.4d; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4d Number and Percentage of Subjects with Hematology Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Hemoglobin	High: ≥ 18.5 g/dL (males) ≥ 16.5 g/dL (females)	(N=54) 1 (2%)	(N=50) 0	(N=45) 0	(N=34) 0
Hematocrit	Low: $\leq 37\%$ (males) $\leq 32\%$ (females)	(N=49) 4 (8%)	(N=47) 3 (6%)	(N=42) 4 (10%)	(N=32) 0
RBC	Low: $\leq 3.8 \times 10^{12}/L$ (males) $\leq 3.5 \times 10^{12}/L$ (females)	(N=53) 0	(N=50) 0	(N=45) 1 (2%)	(N=34) 0
WBC	High: $\geq 16.0 \times 10^9/L$	(N=56) 0	(N=51) 0	(N=45) 0	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Individual subjects with hematology values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.1.

Blood Chemistry Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant blood chemistry values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.2. The percentages of subjects who had blood chemistry values that met the potentially clinically significant criteria were generally similar among the treatment groups. One subject (4246) in the ABT-594 300 µg BID treatment group had a very high glucose on Day 14 (334 mg/dL) and was prematurely discontinued from study drug due to hyperglycemia. However, the

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

92

subject's glucose was high (229 mg/dL) at baseline, indicating poor control of her diabetes. The percentages of subjects who developed blood chemistry values that met the potentially clinically significant criteria are presented in Table 12.4e; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4e Number and Percentage of Subjects with Blood Chemistry Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Glucose	High: ≥ 175 mg/dL	(N=33) 19 (58%)	(N=23) 16 (70%)	(N=28) 16 (57%)	(N=20) 7 (35%)
	Low: ≤ 45 mg/dL	0	1 (4%)	0	0
Uric Acid	High: ≥ 10.5 mg/dL (males)	(N=56) 0	(N=51) 0	(N=42) 0	(N=34) 1 (3%)
	≥ 8.5 mg/dL (females)				
BUN	High: ≥ 30 mg/dL	(N=56) 2 (4%)	(N=51) 1 (2%)	(N=43) 0	(N=34) 1 (3%)
Creatinine	High: ≥ 2.0 mg/dL	(N=57) 0	(N=51) 1 (2%)	(N=45) 0	(N=35) 0
Chloride	Low: ≤ 90 mEq/L	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Calcium	Low: ≤ 8.2 mg/dL	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Triglycerides	High: ≥ 600 mg/dL	(N=54) 2 (4%)	(N=43) 0	(N=40) 2 (5%)	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.2 and Appendices 16.2__8.3.1 through 16.2__8.3.5

Individual subjects with blood chemistry values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.2.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066089

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

93

Urinalysis Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant urinalysis values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.3. The percentages of subjects who had urinalysis values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed urinalysis values that met the potentially clinically significant criteria are presented in Table 12.4f; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4f Number and Percentage of Subjects with Urinalysis Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Urine Glucose	High: $\geq 3+$ ^a	(N=50) 12 (24%)	(N=44) 12 (27%)	(N=41) 10 (24%)	(N=27) 5 (19%)
Urine Protein	High: $\geq 3+$ ^a / ≥ 10	(N=56) 0	(N=50) 0	(N=45) 0	(N=32) 1 (3%)
Urine Ketones	High: $\geq 3+$ ^a	(N=57) 1 (2%)	(N=50) 0	(N=45) 0	(N=32) 0
Urine RBCs	High: ≥ 8 /hpf (male) ≥ 10 /hpf (female)	(N=57) 2 (4%)	(N=50) 3 (6%)	(N=44) 0	(N=31) 2 (6%)
Urine WBCs	High: ≥ 10 /hpf $\geq 2+$	(N=55) 4 (7%)	(N=50) 2 (4%)	(N=45) 3 (7%)	(N=32) 4 (13%)
hpf = high power field.					
^a $\geq 3+$ on a scale with 4+ being the maximum value.					

Cross Reference: Table 14.3.4__4.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

Individual subjects with urinalysis values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.3.

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066090

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

94

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Listing of Individual Measurements by Subject and Each Abnormal Value

The location of vital sign, physical findings, and safety data is presented below.

Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing Appendix
Physical Examination	None	None	16.2__4.4
Vital Signs	14.3.5__1	14.3.5__2 14.3.5__3	16.2__9.1
ECGs	14.3.6__1 14.3.6__2	14.3.6__3 14.3.6__4	16.2__9.2

No normal reference range was used for evaluating vital sign or ECG variables. Criteria for potentially clinically significant values (i.e., Very High or Very Low values) for vital signs and ECG are presented in Table 14.3.4__1.0.

12.5.2 Findings on Physical Examination

Clinically significant deteriorations from baseline physical examination were captured as adverse events (Appendices 16.2__4.4 and 16.2__7.1.1).

12.5.3 Vital Signs Evaluation

12.5.3.1 Vital Signs Values Over Time

Statistically significant differences were observed between treatment groups for mean change from baseline to minimum and/or maximum; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for vital sign parameters is presented in Table 12.5a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

95

Table 12.5a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Vital Sign Parameters

Vital Sign Parameter (units)	Treatment Group			
	Placebo (N=62)	ABT-594		
		150 µg BID (N=62)	225 µg BID (N=66)	300 µg BID (N=64)
Systolic Blood Pressure (mm Hg)				
Baseline Mean	130.8	134.3	136.8	133.9
Mean Change to Maximum	11.8	8.6	3.9*	7.6
Diastolic Blood Pressure (mm Hg)				
Baseline Mean	76.3	78.7	77.6	76.5
Mean Change to Maximum	6.4	4.5	2.7*	4.6
Mean Change to Final	1.4	-3.2*	-1.5	0.8
Heart Rate (bpm)	(N=62)	(N=61)	(N=66)	(N=63)
Baseline Mean	76.1	75.4	75.2	76.1
Mean Change to Final	2.5	-1.8*	2.0	0.6
Weight (pounds)	(N=61)	(N=60)	(N=62)	(N=60)
Baseline Mean	204.0	199.8	199.1	204.1
Mean Change to Minimum	-0.1	-2.1*	-1.9*	-2.8*
Mean Change to Maximum	1.8	0.0*	-0.1*	-1.4*
Mean Change to Final	1.1	-0.8*	-1.0*	-2.0*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.5__1 and Appendix 16.2__9.1

12.5.3.2 Individual Subject Changes

Criteria for potentially clinically significant vital signs and weight values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.5__3. The percentages of subjects who had vital signs values that met the potentially clinically significant criteria were generally similar among the treatment groups. A very high sitting systolic blood pressure value was reported by 0 placebo-treated subjects, 6% (3/50) of ABT-594 150 µg-treated subjects, 0 ABT-594 225 µg-treated subjects, and 3% (1/36) of ABT-594 300 µg BID-treated subjects (Table 14.3.5__3).

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
 ABBT0066092

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

96

12.5.4 Electrocardiogram Evaluation

12.5.4.1 ECG Values Over Time

No statistically significant differences were observed between placebo and any of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value for ECG variables (Table 14.3.6__1).

12.5.4.2 Individual Clinically Significant Abnormalities

The percentage of subjects with shifts in ECG parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.6__2. The majority of subjects had ECG values within normal range at the Baseline and Final Visits.

12.5.4.3 Individual Clinically Significant Abnormalities

Criteria for potentially clinically significant ECG values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.6__4. The percentages of subjects who had ECG values that met the potentially clinically significant criteria were generally similar among the treatment groups. Of note, the high QT_C interval in an ABT-594 225 µg BID-treated subject (4081) was an isolated occurrence that was not associated with an adverse event. The percentages of subjects who developed ECG values that met the potentially clinically significant criteria are presented in Table 12.5b; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

97

Table 12.5b Number and Percentage of Subjects with ECG Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
QT _C Interval ^a		(N=49)	(N=41)	(N=30)	(N=21)
	High: ≥500 msec	0	0	1 (3%)	0
PR Interval		(N=44)	(N=41)	(N=30)	(N=20)
	High: ≥210 msec	1 (2%)	0	1 (3%)	0
Heart Rate		(N=50)	(N=41)	(N=31)	(N=21)
	High: ≥120 bpm and increased ≥30 bpm from baseline	0	0	2 (6%)	0

^a QT_C calculated as QT divided by the square root of RR interval.

Cross Reference: Table 14.3.6__4 and Appendix 16.2__9.2

Individual subjects with ECG values that met the potentially clinically significant criteria are summarized in Table 14.3.6__3.

12.6 Safety Conclusions

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and

CONFIDENTIAL INFORMATION - ABBOTT LABORATORIES
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

Confidential
ABBT0066094

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

98

300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

99

13.0 Discussion and Overall Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

100

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

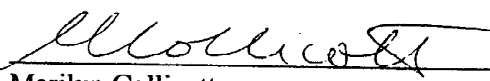
PART 1

ABBOTT LABORATORIES
Clinical Protocol

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the
Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients
with Pain Associated with Osteoarthritis of the Knee**

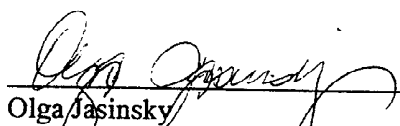
Protocol M98-826

Incorporating Amendment Numbers One and Two - December 22, 1998



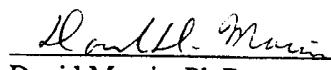
Marilyn Collicott
Senior Clinical Research Associate, Analgesia Venture

12/22/98
Date



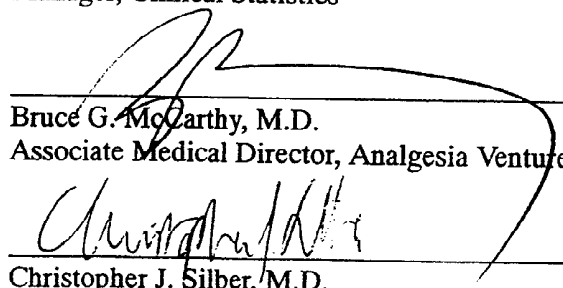
Olga Jasinsky
Sr. Operations Manager, Analgesia Venture

12-22-98
Date



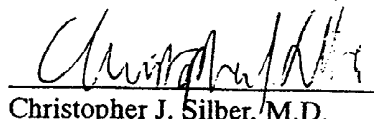
David Morris, Ph.D.
Manager, Clinical Statistics

12-23-98
Date



Bruce G. McCarthy, M.D.
Associate Medical Director, Analgesia Venture

12/22/98
Date



Christopher J. Silber, M.D.
Venture Head, Analgesia Venture

12/22/98
Date

 **Abbott Laboratories**

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABBOTT LABORATORIES
CLINICAL PROTOCOL
INVESTIGATIONAL NEW DRUG
ABT-594

PROTOCOL M98-826

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the
Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients
with Pain Associated with Osteoarthritis of the Knee**

Amendment Two - December 22, 1998

The purpose of this revision is to:

- Delete inclusion criteria that specifies patients must be non-smokers and non-nicotine users.
- Remove reference to nicotine use throughout the protocol.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Amendment Two - December 22, 1998

2

The specific changes are as follows:

Specific Protocol Changes:

**Section 2.0 Study Synopsis, Diagnosis and Main Criteria for Inclusion,
Fourth Bullet Point**

Delete:

- The patient must be a non-smoker or not have smoked or used nicotine by other means (i.e., chewing tobacco, nicotine gum or patch) within two months before dosing.

Section 9.3.1 Inclusion Criteria, Subsections 9.3.1.5

Delete:

- 9.3.1.5 The patient must be a non-smoker or not have smoked or used nicotine by other means (i.e., chewing tobacco, nicotine gum or patch) within two months before dosing.

Re-number subsections that follow 9.3.1.5.

Section 9.4.7 Prior and Concomitant Therapy, Second Paragraph

Delete:

Patients, who have used nicotine-containing products within two months of randomization, will not be eligible for inclusion in this study. Patients will not be allowed to use nicotine-containing products during this study.

Section 9.5.1.2 Safety Measurements and Procedures, Medical History, Last Sentence

Change:

The medical history (including medication and nicotine use) will be updated at the Baseline Visit (Day 1).

To read:

The medical history will be updated at the Baseline Visit (Day 1).

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

1.0 Title Page

Abbott Laboratories
Analgesia Venture, D48Q
Clinical Study

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety
and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain
Associated with Osteoarthritis of the Knee**

ABT-594/M98-826

Development Phase: II

Investigators: Multicenter Trial

Date First Patient Dosed: October 1998

Date Last Patient Completed Dosing: February 1999

Sponsor/Emergency Contact: Christopher J. Silber, M.D.
Venture Head,
Analgesia Venture
Phone: (847) 938-5236, Fax: (847) 938-5258
Analgesia Venture, Department 48Q
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

This study will be conducted in compliance with Good Clinical Practice, including
the archiving of essential documents.

Confidential Information

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

CONFIDENTIAL INFORMATION ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

ii

2.0 Study Synopsis

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Item of the Submission: Not applicable (N/A) Volume: N/A Page: N/A	<i>(For National Authority Use Only)</i>
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain Associated with Osteoarthritis of the Knee		
Investigator(s): Multicenter Study		
Study Center(s): Multicenter Study		
Publication (reference): N/A		
Study Period (years): Estimated Date of First Enrollment: 10/98 Estimated Date of Last Enrollment: 2/99	Phase of Development: II	
Objectives: The objective of this study is to compare the safety and analgesic efficacy of 25 µg, 50 µg and 75 µg twice daily (BID) of ABT-594 and ibuprofen 400 mg three times a day (TID) to placebo in patients who have pain associated with radiographic Grade II or III primary osteoarthritis of the knee, have moderate or severe pain (by the four point Daily Pain Intensity Categorical Scale) everyday during the Baseline Assessment Period, have moderate or severe pain (by the four point Pain Intensity Categorical Scale at Rest) during the Baseline Visit and who are not taking another analgesic concurrently.		
Methodology: This is a Phase II, randomized, double-blind, placebo-controlled, active-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in patients with pain associated with osteoarthritis of the knee. Approximately 250 patients will be assigned randomly in equal numbers to receive either ABT-594 BID (25 µg, 50 µg or 75 µg), ibuprofen TID (400 mg), or placebo for 22 days on an outpatient basis. Approximately 15 sites will be recruited in order to enroll 250 patients who meet entry criteria for this study.		

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

iii

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Item of the Submission: Not applicable (N/A) Volume: N/A Page: N/A	<i>(For National Authority Use Only)</i>
Methodology: (Continued) <p>Prior to study drug administration, patients will have discontinued all analgesic medications and have completed a 3 day Washout Period and a 3 day Baseline Pain Assessment Period. Patients will then receive study medication for 22 days (Treatment Phase), during which time they will return to the site weekly (Treatment Visits I, II and III). During the Pre-Treatment and Treatment Phases, patients will be allowed to take limited and monitored amounts of analgesic rescue medication (acetaminophen), except for the 48 hours prior to Baseline and Treatment Visits. Patients will complete diary-based assessments of their knee pain each day from the three days prior to study drug administration (Baseline Pain Assessment Period) through Day 21 of study drug administration. In addition, patients will undergo site-based assessments of their knee pain at the Baseline Visit and Treatment Visits I, II and III. Patients will discontinue study drug administration after Treatment Visit III and return to the site for the Follow-Up visit 7-10 days later. See Figure 9.1a, Study Schematic, for additional study layout information.</p> <p>Diary-based assessments will include the Daily Pain Intensity Categorical Scale and the Daily Pain Intensity VAS. Site-based assessments will include the Pain Intensity Categorical Scale and VAS (each at rest and after walking), the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) version 3.0 and the Patient Global Evaluation (the latter only at Treatment Visit III).</p>		
No. of Patients: 250		
Diagnosis and Main Criteria for Inclusion: <p>A patient may be randomized in this study provided that he/she meets all of the inclusion criteria outlined below and does not meet any of the exclusion criteria in Section 9.3.2.</p> <ul style="list-style-type: none"> • The patient must be between the ages of 18 and 75 years of age, inclusive. • The patient's weight must be between 100 lbs and 265 lbs, inclusive, with weight proportional to height as judged by the investigator. • A female patient must be non-lactating and: <ul style="list-style-type: none"> - of non-childbearing potential (either postmenopausal for at least one year or surgically sterile, including tubal ligation), <p>OR</p> <ul style="list-style-type: none"> - of childbearing potential using oral or barrier contraceptive methods for at least two months preceding randomization (and must continue contraceptive method through the course of the study). <p>All female patients must have a negative β subunit human chorionic gonadotropin (β-hCG) at the screening, baseline and treatment visits.</p>		

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

iv

Name of Company: Abbott Laboratories	Individual Study Table Referring to Item of the Submission: Not applicable (N/A)	<i>(For National Authority Use Only)</i>
Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC)	Volume: N/A	
Name of Active Ingredient: ABT-594	Page: N/A	

Diagnosis and Main Criteria for Inclusion: (Continued)

- The patient must have a diagnosis of primary osteoarthritis.
- The patient must have pain while standing, walking or on motion for the last 25 out of 30 days prior to the Screening Visit, osteophytes on knee radiograph (within the last 6 months) and at least one of the following: age greater than 50 years, knee stiffness less than 30 minutes in the morning or knee crepitus on active motion of the knee.
- The patient must have grade II or grade III osteoarthritis of the knee by radiograph, as adapted from the Council for International Organization of Medical Science 1963 (Appendix G).
- The patient must have moderate or severe pain (by the four point Daily Pain Intensity Categorical Scale) everyday during the Baseline Assessment Period and have moderate or severe pain (by the four point Pain Intensity Categorical Scale at Rest) during the Baseline Visit.
- The patient must be able to walk without assistance or assistive devices (cane, crutches or walkers).

Test Product(s): ABT-594 25 µg and 50 µg SEC.

Dose: ABT-594 25 µg, 50 µg, or 75 µg BID (Section 9.4.1)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
ABT-594 25 µg SEC	39-904-AR-R1
ABT-594 50 µg SEC	39-905-AR-R1

Duration of Treatment: 22 days

Reference Therapy:

Placebo: Placebo for ABT-594 SEC;
 Placebo for ibuprofen capsule

Active: Ibuprofen 200 mg capsule

Reference Therapy: (Continued)

Dose:

Placebo: Placebo to match test product or active comparator (Section 9.4.1)

Active: Ibuprofen 400 mg (Section 9.4.1)

Mode of Administration: Oral

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

v

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Item of the Submission: Not applicable (N/A) Volume: N/A Page: N/A	<i>(For National Authority Use Only)</i>								
Batch Number: <table border="1" data-bbox="345 720 1057 945"> <thead> <tr> <th>Study Drug</th> <th>Drug Product Lot Number</th> </tr> </thead> <tbody> <tr> <td>Placebo for ABT-594 SEC</td> <td>39-903-AR-R1</td> </tr> <tr> <td>Placebo for ibuprofen capsule</td> <td>40-913-AR-AA</td> </tr> <tr> <td>Ibuprofen 200 mg capsule</td> <td>31-782-AR-03</td> </tr> </tbody> </table>			Study Drug	Drug Product Lot Number	Placebo for ABT-594 SEC	39-903-AR-R1	Placebo for ibuprofen capsule	40-913-AR-AA	Ibuprofen 200 mg capsule	31-782-AR-03
Study Drug	Drug Product Lot Number									
Placebo for ABT-594 SEC	39-903-AR-R1									
Placebo for ibuprofen capsule	40-913-AR-AA									
Ibuprofen 200 mg capsule	31-782-AR-03									
Analgesic Rescue Medication: Acetaminophen 500 mg caplet Dose: Acetaminophen 500 mg (Section 9.4.1) Mode of Administration: Oral Batch Number: TBD										
Criteria for Evaluation Efficacy: Daily Pain Intensity (four-point categorical scale and VAS, both diary-based), Pain Intensity at rest and after walking (four-point categorical scale and VAS, both site-based), WOMAC VA 3.0 Index, Patient Global Evaluation, and rescue medication use. Safety: Medical history, physical exam, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.										

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

vi

Name of Company: Abbott Laboratories	Individual Study Table Referring to Item of the Submission: Not applicable (N/A)	<i>(For National Authority Use Only)</i>
Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC)	Volume: N/A	
Name of Active Ingredient: ABT-594	Page: N/A	
Statistical Methods: <p>For all safety and efficacy analyses, the primary comparison will be between ABT-594 and placebo.</p> <p>Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the treatment groups using ANOVA and Fisher's exact test, as appropriate.</p> <p>Treatment emergent adverse events will be summarized by body system and COSTART term and compared using Fisher's exact test.</p> <p>The primary and secondary efficacy variables, including change from baseline pain scores and change from baseline to the total and three subscales of WOMAC index (pain, stiffness, and physical function), will be analyzed by using appropriate parametric and nonparametric methods. The final global evaluation score will be compared using Cochran-Mantel-Haenszel methodology. Average daily dose and percent of days using analgesic rescue medication will be analyzed using appropriate ANOVA models.</p> <p>Dose response for ABT-594 will be explored, with placebo included and without placebo. Other efficacy analyses will be performed as appropriate.</p> <p>Laboratory data, ECG and vital signs that are very low or high will be flagged in the data listings. In addition, all potentially clinically significant values will be identified.</p>		

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

vii

3.0 Table of Contents

	Page
1.0 Title Page	i
2.0 Study Synopsis	ii
3.0 Table of Contents	vii
4.0 List of Abbreviations and Definitions of Terms	xi
5.0 Ethics	1
5.1 Institutional Review Board or Independent Ethics Committee ..	1
5.2 Ethical Conduct of the Study	1
5.3 Patient Information and Consent	1
5.4 Patient Confidentiality	2
6.0 Investigators and Study Administrative Structure	3
6.1 Investigative Sites	3
6.2 Sponsor Information	3
6.3 Contract Research Organization	3
6.4 Clinical Supply Management	3
6.5 Central Laboratory	4
6.6 Administrative Structure	5
7.0 Introduction	6
7.1 Analgesia Today	6
7.2 ABT-594	6
8.0 Study Objectives	10
9.0 Investigational Plan	10
9.1 Overall Study Design and Plan: Description	10
9.2 Discussion of Study Design, Including the Choice of Control Groups	15
9.3 Selection of Study Population	16

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 2

ABT-594

Protocol M98-826

Incorporating Amendment Numbers One and Two - 12/22/98

viii

Table of Contents

(Continued)

	Page
9.3.1 Inclusion Criteria	16
9.3.2 Exclusion Criteria	17
9.3.3 Removal of Patients from Therapy of Assessment	19
9.4 Treatments	20
9.4.1 Treatments Administered	20
9.4.2 Identity of Investigational Products	21
9.4.2.1 Packaging and Labeling	22
9.4.2.2 Storage and Disposition of Supplies	23
9.4.2.3 Drug Accountability	23
9.4.3 Method of Assigning Patients to Treatment Groups	24
9.4.4 Selection of Doses in the Study	24
9.4.5 Selection and Timing of Dose for Each Patient	24
9.4.6 Blinding	25
9.4.7 Prior and Concomitant Therapy	25
9.4.8 Treatment Compliance	26
9.5 Efficacy, Pharmacokinetics and Safety Variables and Other Study Procedures	27
9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts	27
9.5.1.1 Efficacy Measurements	30
9.5.1.2 Safety Measurements and Procedures	31
9.5.1.2.1 Adverse Events	36
9.5.1.2.2 Serious Adverse Events	38
9.5.2 Appropriateness of Measurements	40
9.5.3 Efficacy Variables	40
9.5.3.1 Primary Variable	41

CONFIDENTIAL INFORMATION ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

ix

Table of Contents

(Continued)

	Page
9.5.3.2 Secondary Variables	41
9.5.4 Drug Concentration Measurements	41
9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay	41
9.5.4.2 Shipment of Plasma Samples	42
9.5.5 Blood Samples for Genetic Polymorphism Analysis	42
9.6 Data Quality Assurance	43
9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size	44
9.7.1 Statistical and Analytical Plans	44
9.7.1.1 Data Sets Analyzed	45
9.7.1.2 Demographic and Other Baseline Characteristics	45
9.7.1.3 Efficacy Analyses	45
9.7.1.4 ABT-594 Plasma Assay	47
9.7.1.5 Safety	47
9.7.2 Determination of Sample Size	48
9.8 Changes in the Conduct of the Study or Planned Analyses	48
9.8.1 Protocol Changes	48
10.0 Protocol Deviations	49
11.0 Use of Information and Publication	49
12.0 Completion of The Study	50
13.0 Investigator's Agreement	51
14.0 References	52

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

x

Table of Contents (Continued)

Page

List of Tables

Table 9.4.1a	Number and Type of Capsules by Treatment Regimen	20
Table 9.4.2a	Identity of Investigational Products	21
Table 9.5a	Study Procedures Flow Chart	28
Table 9.5b	Clinical Laboratory Tests	34
Table 9.5c	Definitions for Investigator Rating of Adverse Event Severity	37
Table 9.5d	Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug	37

List of Figures

Figure 6.6a	Administrative Structure	5
Figure 9.1a	Study Schematic	14

List of Appendices

Appendix A	Documents Required Prior to Initiation of the Study	53
Appendix B	Declaration of Helsinki	54
Appendix C	Responsibilities of the Clinical Investigator	58
Appendix D	Elements of the Consent Form	59
Appendix E	Sample Abbott Laboratories Drug Accountability Form . .	62
Appendix F	Pain Assessments	63
Appendix G	Osteoarthritis Severity Grades for Knee and Hip Joints Adapted from the Council for International Organizations of Medical Sciences 1963	66
Appendix H	The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Version VA3.0	67
Appendix I	Potentially Clinically Significant Values for Laboratory Determinations, Vital Signs and Electrocardiogram Variables	73

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

xi

4.0 List of Abbreviations and Definitions of Terms

Abbreviations

ABT-594	[(R)-5-(2-azetidylmethoxy)-2-chloropyridine] or A-165594
ANOVA	Analysis of Variance
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
BID	<i>bis in die</i> , twice a day
bpm	Beats per minute
BUN	Blood urea nitrogen
°C	Degrees Centigrade
cc	Cubic centimeter
Cont.	Continued
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CSI	Clinical Supplies Invoice
D	Day
dL	Deciliter
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EEC	European Economic Community
FDA	Food and Drug Administration
°F	Degrees Fahrenheit
fL	Femtoliter
g	Gram
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
hpf	High Powered Field
hrs	Hours
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International units
kg	Kilogram

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

xii

List of Abbreviations and Definitions of Terms (Continued)

L	Liter
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
µg/mcg	Microgram
mEq	Milliequivalents
mg	Milligrams
min	Minutes
mL	Milliliter
mm	Millimeter
mm Hg	Millimeters of mercury
msec	Millisecond
N/A	Not applicable
nAChRs	Neuronal nicotinic acetylcholine receptors
NPRO	New Product Research Order
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OC	Observed cases
OTC	Over-the-counter
PPD	Pharmaceutical Products Division
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SEC	Soft Elastic Capsule
sec	Second
SOP	Standard Operating Procedure
STD	Standard Deviation
TCA	Tricyclic antidepressant
TID	<i>ter in die</i> , three times a day
ULN	Upper limit of normal
VA	Visual Analog

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

xiii

List of Abbreviations and Definitions of Terms
(Continued)

VAS	Visual Analog Scale
WBC	White blood cell
WOMAC	The Western Ontario and McMaster Universities Osteoarthritis Index

Terms

AUC	Area under the plasma concentration-time curve
C _{max}	Maximum observed concentration
NOMAD®	A validated data management system

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-F2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

1

5.0 Ethics

5.1 Institutional Review Board or Independent Ethics Committee

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human patients in research. The investigator will obtain a duly constituted IRB review and approval of the protocol, informed consent form and all other forms of patient information related to the study (e.g., advertisements used to recruit patients). Abbott Laboratories will receive documentation of the study approval, the signed signature page from the study protocol, patient informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year. A complete list of documents required prior to initiation of the study is located in Appendix A.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version, Appendix B) and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix C.

5.3 Patient Information and Consent

The investigator or his/her representative will explain the nature of the study to the patient, and answer all questions regarding this study. Prior to any screening procedures being performed on the patient, the informed consent statement will be reviewed and signed and dated by the patient and the person who administered the informed consent.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

2

A copy of the informed consent form will be given to the patient and a copy will be placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the patient received a signed copy. Elements of an Informed Consent are specified in Appendix D.

5.4 Patient Confidentiality

All reports and communications relating to patients in the study will identify each patient only by the patient's initials (first, middle, last) and by the patient's study number. Case report forms (CRF) will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the patient's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the CRFs.

The site will collect information on the patient per International Council on Harmonization (ICH) requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency should also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site according to the record retention guidelines outlined in Section 12.0.

Neither the patient, the patient's physician, nor the investigator will be informed of the patient's pharmacogenetic results, should they be obtained. If performed, results from individual patients will be kept confidential and will not be given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples will be stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples will be kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

3

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Investigative sites will be selected by Abbott Laboratories and the Contract Research Organization (CRO). Abbott Laboratories will give final approval for all sites. Approximately 15 sites will be selected to enroll patients for this study. Investigators will be selected on their ability to enroll patients as well as the adequacy of their sites to manage study related activities and requirements.

6.2 Sponsor Information

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this multicenter clinical study. The protocol, CRFs and sample informed consent form will be generated by Abbott Laboratories. The database for this study will be created using NOMAD®, a validated data management system. Designated statisticians from Abbott Laboratories will be responsible for the statistical analysis of the data.

6.3 Contract Research Organization

Abbott Laboratories will assign prestudy and initiation visits, site monitoring, and post-study site visits to a CRO for the conduct of this clinical study. The sponsor and CRO will maintain contact in order to manage adequately the progress of the study. The CRO will coordinate and perform all site visits and will prepare trip reports, using the Abbott format, for each visit performed. These reports will detail the activities conducted at all investigative sites and will include all relevant observations. All trip reports will be forwarded to the sponsor in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures (SOP).

6.4 Clinical Supply Management

Clinical supplies will be prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories will authorize the release of clinical supplies once the appropriate essential documents have

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 3

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

4

been received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs. The site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records (Appendix E), and records for return of used and unused clinical supplies to Abbott Laboratories. Monitors will check drug accountability records regularly.

6.5 Central Laboratory

This study will utilize one central laboratory. All protocol specified clinical laboratory tests will be performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

5

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

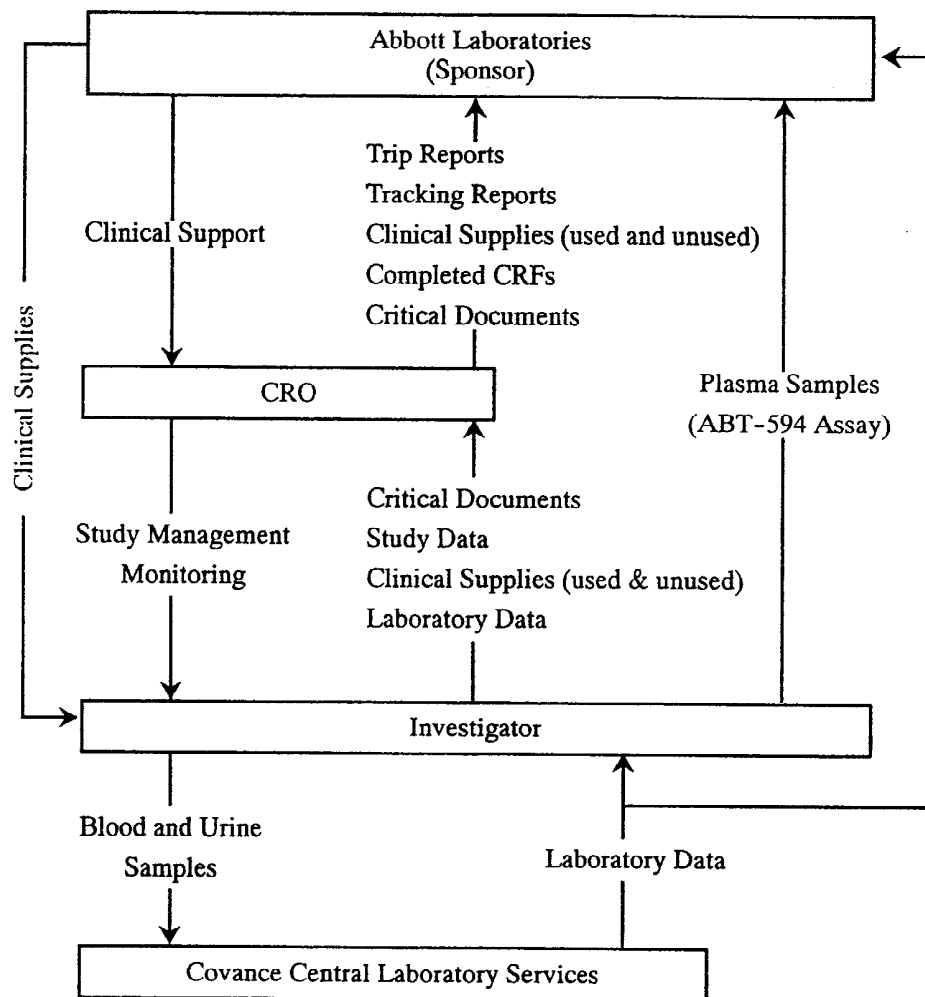


Figure 6.6a Administrative Structure

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

6

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. In the United States, millions of operations are performed annually, most involving some form of acute pain management. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹ For patients with cancer, it has been estimated that pain is experienced by 20% to 50% of patients at the time of their diagnosis, with up to 75% of those with advanced cancer experiencing pain.²

Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in patients receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (\pm)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

7

morphine in rodent models of antinociception.³ The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.⁴ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

8

To date, four completed Phase I studies have evaluated the safety, tolerability, and pharmacokinetics of ABT-594 single dose (Study M97-676) and multiple dose (Study M97-743) administration, the effect of food on the bioavailability of single doses of ABT-594 oral solution (Study M97-787) and soft elastic capsule (SEC) formulations (Study M97-706), and the comparative bioavailability of these initial oral liquid and solid soft elastic capsule (SEC) formulations (Study M97-706). In these studies, approximately 151 subjects have received at least one dose of ABT-594 (25 µg to 200 µg) under fasted (i.e., after a 10-hour fast) or fed conditions (i.e., approximately 30 minutes after a meal was served).

In Study M97-676, a double-blind, placebo-controlled single rising dose study, 53 subjects in eight dosing groups received a single fixed dose of an oral solution of ABT-594 (30 µg to 200 µg) under fasted or fed conditions. Twenty-four placebo subjects were also involved in the study. In each dose group, up to seven subjects received ABT-594 and three subjects received placebo. Thirty-five normal healthy males received either 30 µg, 50 µg, 80 µg, 100 µg, or 150 µg of ABT-594 under fasted conditions. Thirteen normal healthy males received either 150 µg or 200 µg of ABT-594 under fed conditions. Five surgically-sterilized females received 80 µg of ABT-594 under fed conditions.

Dosing in males could not proceed beyond the 150 µg level under fasted conditions due to emesis, but the 150 µg dose administered under fed conditions was well tolerated. Approximately 60% of ABT-594 subjects and 50% of placebo subjects experienced at least one adverse event. The most frequently noted adverse events were dizziness, nausea, headache, vomiting, pallor, somnolence, sweating, diarrhea, paresthesia, vasodilation, and vertigo. Events of headache, vasodilation, diarrhea, and vertigo were evident at comparable levels in placebo subjects. Pharmacokinetic analysis suggests that ABT-594 shows relatively linear pharmacokinetics at doses up to 150 µg under fasted conditions and that approximately 50% of ABT-594 is excreted in the urine. No effect of gender or feeding condition was evident on pharmacokinetic parameters. ABT-594 was generally well-tolerated at doses up to 100 µg in subjects who were fasted and at 150 µg in subjects who were fed prior to dosing.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

9

In Study M97-743, a double-blind, placebo-controlled multiple rising dose study, 54 normal healthy male subjects in seven dosing groups received a single fixed daily dose of an oral solution of ABT-594 (25 µg to 150 µg) for up to 14 consecutive days under fasted or fed conditions. An additional eight subjects in a twice daily dosing group (Group 8) received two single fixed daily doses, twelve hours apart, of ABT-594 75 µg for up to 14 consecutive days under fed conditions. Thirty-two placebo subjects were also involved in the study. Within each dose group, up to eight subjects received ABT-594 and four subjects received placebo.

Four ABT-594 subjects were prematurely terminated from the M97-743 study. One subject who received a single dose of 75 µg of ABT-594 had a presyncopal episode with pallor, bradycardia, hypotension, and telemetry findings of a 15-second third degree heartblock upon orthostasis, thought to be of possible vasovagal etiology. One subject in the 100 µg fasted dose group was discontinued on Day 8 due to fever and anxiety. In the 100 µg fed dose group, one subject was discontinued on Day 8 due to transaminase elevation greater than three times the upper limit of normal. One subject who received 75 µg of ABT-594 twice daily was discontinued on Day 5 due to sinus tachycardia upon orthostasis.

Initial emesis occurred in four subjects at the 100 µg dose level under fasted conditions, but increased tolerability was noted with repeat dosing and in the 100 µg, 125 µg, and 150 µg dose groups under fed conditions. Approximately 90% of placebo subjects and 89% of ABT-594 subjects had at least one report of an adverse event during the 14-day dosing period. Upon preliminary review, the most frequent events reported for ABT-594 subjects were headache, nausea, dizziness, brief postdosing oral sensation, somnolence, asthenia, vomiting, vasodilation, taste perversion, rhinitis, abnormal thinking, flatulence, paresthesia, sweating, and infection. Other events reported by at least three ABT-594 subjects were injection site pain, orthostatic hypotension, dry mouth, dyspepsia, insomnia, pharyngitis, chest pain, pallor, anorexia, diarrhea, eructation, myalgia, ataxia, epistaxis, abdominal pain, fever, pain, palpitations, hypertonia, incoordination, dyspnea, and dry skin. Events such as headache, somnolence, rhinitis, infection, pharyngitis, insomnia, diarrhea, and abdominal pain were also present at a comparable or greater level in placebo subjects.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

10

In Study M97-787, an open-label, two-period crossover study, the effect of food on the bioavailability of an oral solution of ABT-594 after administration of a single 80 µg dose was evaluated in 12 normal healthy male subjects. In Study M97-706, an open-label, four-period study, the comparative bioavailability of three formulations of ABT-594 (liquid, 25 µg and 50 µg SECs) and the effect of food on the SEC bioavailability after administration of single 100 µg doses were evaluated in 24 normal healthy males. In both studies, the preliminary safety and tolerability profile showed no differences from previous studies. In addition, preliminary data suggest bioequivalence between the formulations and no effect of feeding condition on the pharmacokinetic profile of the 50 µg SEC.

Initial Phase I studies have provided preliminary data in support of the safety and tolerability of ABT-594. A Phase II study (M97-772), that will evaluate the analgesic efficacy of ABT-594 in pain after molar extraction, is currently ongoing. This study (M98-826) is one of several additional Phase II studies that will characterize more fully the analgesic efficacy of ABT-594.

8.0 Study Objectives

The objective of this study is to compare the safety and analgesic efficacy of 25 µg, 50 µg and 75 µg twice daily (BID) of ABT-594 and ibuprofen 400 mg three times a day (TID) to placebo in patients who have pain associated with radiographic Grade II or III primary osteoarthritis of the knee, have moderate or severe pain (by the four point Daily Pain Intensity Categorical Scale) everyday during the Baseline Assessment Period, have moderate or severe pain (by the four point Pain Intensity Categorical Scale at Rest) during the Baseline Visit and who are not taking another analgesic concurrently.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This is a Phase II, randomized, double-blind, placebo-controlled, active-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in patients with pain associated with osteoarthritis of the knee. Approximately 250 patients will be

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

11

assigned randomly in an equal ratio to receive one of five treatments: ABT-594 BID (25 µg, 50 µg or 75 µg), ibuprofen TID (400 mg), or placebo for 22 days on an outpatient basis. Approximately 15 sites will be recruited in order to enroll 250 patients who meet entry criteria for this study.

The study will be divided into four phases: Screening Phase (Day -21 to Day -7), Pre-Treatment Phase (Day -6 to Day -1), Treatment Phase (Day 1 to Day 22) and Post-Treatment Phase (Day 23 to Day 32). The Pre-Treatment Phase is further subdivided into the Washout Period (Day -6 to Day -4) and the Baseline Pain Assessment Period (Day -3 to Day -1). Day 1 is the first day of study drug administration. Patients will be allowed a window of ± 1 day for each study visit. The study design is depicted in Figure 9.1a.

Patients will review and sign the informed consent prior to the conduct of any study specific procedures. Patients will then be screened for eligibility by medical history, physical examination, vital sign measurement, electrocardiogram (ECG), clinical laboratory tests and radiographs. A single knee joint will be chosen for all efficacy measures. If both knee joints qualify by entry criteria, then the knee which has been historically more painful for the patient will be studied.

After discontinuing all analgesics (except protocol specified analgesic rescue medication), patients will enter the Pre-Treatment Phase, which will last six days and consist of a Washout Period and a Baseline Pain Assessment Period. The Washout Period will last three days. During the Baseline Pain Assessment Period (Day -3 to Day -1), patients will complete, at approximately 9 P.M. each evening, diary-based assessments of knee pain intensity: the four point Daily Pain Intensity Categorical Scale and the Daily Pain Intensity Visual Analog Scale (VAS, see Appendix F).

On the day after the Baseline Pain Assessment Period, patients will return to the clinic for their Baseline Visit (Day 1). During this visit, patients will undergo an interim history, physical examination, vital sign measurement, ECG and clinical laboratory tests. Study site personnel will also collect patients study diaries. Patients will then complete site-based assessments (prior to study during administration): the Western Ontario and

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

12

McMaster Universities Osteoarthritis Index (WOMAC) Version Visual Analog (VA) 3.0, and the four-point Pain Intensity Categorical Scale and VAS (the latter two scales at rest and after walking). Patients who meet all entry criteria, including moderate or severe pain (by the four point Daily Pain Categorical Scale) everyday during the Baseline Assessment Period and moderate or severe pain (by the four point Pain Intensity Categorical Scale at Rest) during the Baseline Visit, will be randomized in an equal ratio into the following treatment groups: ABT-594 25 µg BID, ABT-594 50 µg BID, ABT-594 75 µg BID, ibuprofen 400 mg TID, or placebo. Patients will also receive their next set of diaries at the Baseline Visit.

Patients will start study drug at the next dosing time on Day 1 (as specified in Section 9.4.5) and continue for a total of 22 days. Patients will complete diary-based assessments each evening (approximately 9 PM), two hours after their evening dose of study drug. They will return to the site for study procedures at the end of Week 1 (Day 8, Treatment Visit I), Week 2 (Day 15, Treatment Visit II) and Week 3 (Day 22, Treatment Visit III). Procedures at Treatment Visits I, II and III will include collection of diaries (and issuance of the next set of diaries at Treatment Visits I and II), site-based assessments (to include the Patient Global Evaluation at Treatment Visit III), physical examination (Treatment Visit III), vital sign measurements, ECG (Treatment Visit III), clinical laboratory tests, and ABT-594 plasma assay sample collection.

During the Pre-Treatment and Treatment Phases, patients will be allowed to take a total of no more than three grams acetaminophen (provided as analgesic rescue medication) per week and no more than one gram acetaminophen in a single day. Patients, however, will not be allowed to take analgesic rescue medication within 48 hours prior to the Baseline Visit and Treatments Visits I, II and III. Patients will record the date, time and number of acetaminophen tablets taken in their diaries.

On the day after Treatment Visit III, patients will enter the Post-treatment Phase. Patients will no longer take study drug or complete pain scales. Patients may re-start all discontinued medication under the guidance of their physician. Patients will return for study procedures at the Follow-up Visit (7-10 days after their final study drug dose). Procedures at the Follow-up Visit will include physical examination, vital sign

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 4

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

13

measurements, the recording of any adverse events and medication use since Treatment Visit III and reexamination of any abnormal findings (by ECG or clinical laboratory tests) present at the previous evaluation.

For those patients who participate in clinical studies of ABT-594 and who consent, a blood sample will be collected in order to obtain a sample of genetic material (DNA). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way patients respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in primary osteoarthritis and pain associated with osteoarthritis.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

14

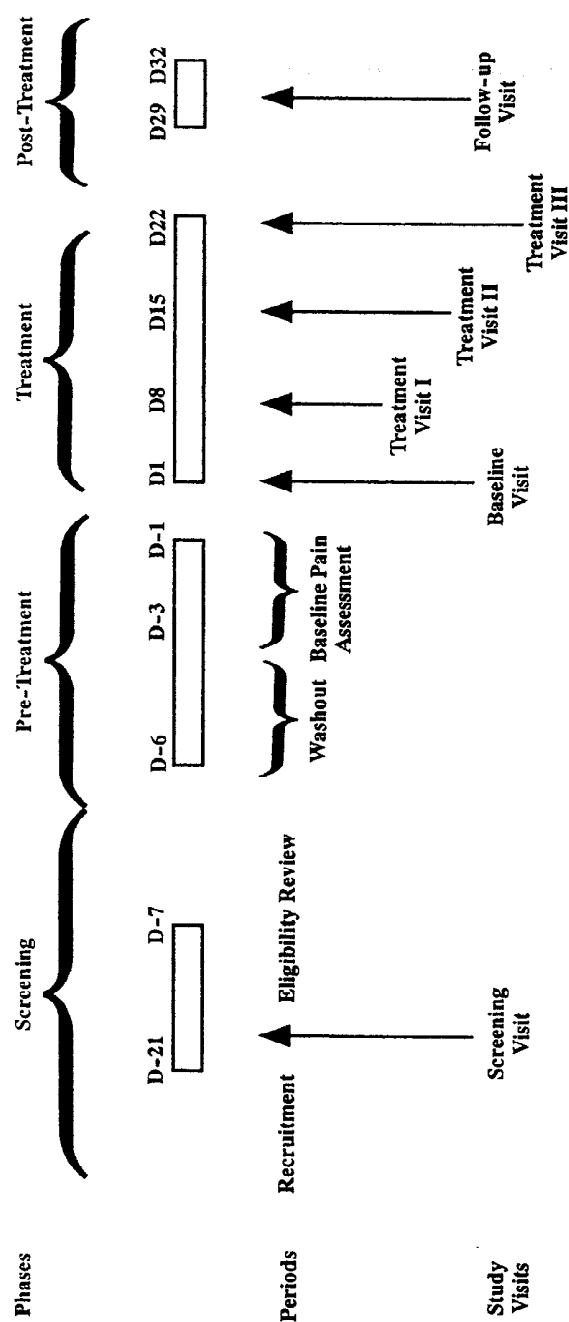


Figure 9.1a Study Schematic

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

15

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provides a placebo control group to assess the analgesic efficacy of ABT-594 and an active control group to assess results of this study in the context of other published osteoarthritis pain research. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain and osteoarthritis function scales will be employed.

The study design includes several similar but distinct efficacy measures in two different settings: diary-based and site-based assessments. Diary-based assessments include the four-point Daily Pain Intensity Categorical Scale and the Daily Pain Intensity VAS. Site-based assessments include the four-point Pain Intensity Categorical Scale and VAS (each at rest and after walking), the WOMAC Index and the Patient Global Evaluation (the latter only at Treatment Visit III). Diary-based pain intensity (Daily Pain Intensity) measurements assess pain over the preceding 24 hours, while the site-based pain intensity measurements assess pain at the time of measurement. The WOMAC Index and Patient Global Evaluation assess variables over longer time frames.

This study is similar in design (including length of study and measures of efficacy and safety) to previously published studies of pain relief in osteoarthritis, especially studies of NSAIDs. It includes, however, diary-based pain assessments (described above) that are less common in osteoarthritis studies but more common in other pain studies.

A washout period is included because the patients sought for inclusion in this study are likely to be taking analgesic medications prior to study start. Patients are unlikely, however, to tolerate moderate or severe pain for extended periods necessary to achieve a complete washout and the three day Washout Period represents a compromise.

Ibuprofen (400 mg TID) has been chosen as the active control. Ibuprofen is indicated for the relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis. Ibuprofen represents a reasonable active control because its efficacy and adverse events in osteoarthritis are well understood.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

16

9.3 Selection of Study Population

It is anticipated that approximately 250 patients will be randomized and receive study medication in this study. A patient may be randomized in this study provided that he/she meets all of the inclusion criteria outlined in Section 9.3.1 and does not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

- 9.3.1.1 Prior to any study specific procedure, voluntary written informed consent must be obtained from the patient after the purpose and nature of the study have been explained.
- 9.3.1.2 The patient must be between the ages of 18 and 75 years of age, inclusive.
- 9.3.1.3 The patient's weight must be between 100 lbs and 265 lbs, inclusive, with weight proportional to height as judged by the investigator.
- 9.3.1.4 A female patient must be non-lactating and:
 - of non-childbearing potential (either postmenopausal for at least one year or surgically sterile, including tubal ligation),OR
 - of childbearing potential using oral or barrier contraceptive methods for at least two months preceding randomization (and must continue contraceptive method through the course of the study).

All female patients must have a negative β subunit human chorionic gonadotropin (β -hCG) at the screening, baseline and treatment visits.

- 9.3.1.5 The patient must have pain while standing, walking or in motion for the last 25 out of 30 days prior to the Screening Visit, osteophytes on knee radiograph (within the last 6 months) and at least one of the following: age greater than 50 years, knee stiffness less than 30 minutes in the morning or knee crepitus during active motion of the knee.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

17

- 9.3.1.6 The patient must have a diagnosis of primary osteoarthritis.
- 9.3.1.7 The patient must have grade II or grade III osteoarthritis of the knee by radiograph, as adapted from the Council for International Organization of Medical Science 1963 (Appendix G).
- 9.3.1.8 The patient must have moderate or severe pain (by the four point Daily Pain Intensity Categorical Scale) everyday during the Baseline Assessment Period and have moderate or severe pain (by the four point Pain Intensity Categorical Scale at Rest) during the Baseline Visit.
- 9.3.1.9 The patient must be able to walk without assistance or assistive devices (cane, crutches or walkers).

9.3.2 Exclusion Criteria

- 9.3.2.1 The patient has positive test results for drugs of abuse at the Screening or Baseline Visits, viral hepatitis at the Screening Visit, or has a known history of a positive test result for HIV.
- 9.3.2.2 The patient has a history of drug and alcohol abuse or dependence.
- 9.3.2.3 The patient consumes more than two alcoholic drinks each day (where an alcoholic drink is 4 ounces of wine, 10 ounces of 5.7% beer or a 1.25 ounce shot of 80 proof liquor) by patient history.
- 9.3.2.4 The patient has a history of epilepsy, any clinically significant cardiac, respiratory (except mild asthma), renal, hepatic, gastrointestinal, hematologic, or psychiatric disease or disorder, or any uncontrolled medical illness.
- 9.3.2.5 The patient has received an investigational drug within thirty (30) days prior to administration of study treatment or is scheduled to receive an investigational drug other than ABT-594 during the course of this study.
- 9.3.2.6 The patient has a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

18

- 9.3.2.7 The patient has orthostatic hypotension at the Screening Visit (as defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after one minute of standing), or a history of syncope or pre-syncope symptoms.
- 9.3.2.8 The patient has a history of nasal polyps, bronchospasm, angioedema, gastrointestinal or other difficulties induced by NSAIDs.
- 9.3.2.9 The patient has a history of ulcer, peptic ulcer disease, gastritis, gastrointestinal bleed or liver disease.
- 9.3.2.10 The patient has a history of hypersensitivity to NSAIDs, acetaminophen or nicotinic agents.
- 9.3.2.11 The patient has participated previously in a study involving ABT-594, including the present study.
- 9.3.2.12 The patient has a clinically significant abnormality in clinical chemistry, hematology, or urinalysis, including AST or ALT ≥ 1.5 the upper limit of the reference range or calculated creatinine clearance ≤ 60 mL/minute.
- 9.3.2.13 The patient has clinically significant electrocardiographic abnormalities.
- 9.3.2.14 The patient has a diagnosis of secondary arthritis.
- 9.3.2.15 The patient has had a history of trauma to the knee joint under study within one year before the Screening Visit.
- 9.3.2.16 The patient has undergone arthroscopy of the knee joint under study within one year before the Screening Visit or any other type of surgery to the knee at any time.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

19

- 9.3.2.17 The patient has had a hyaluronic acid injection within one year before the Screening Visit.
- 9.3.2.18 The patient has taken chondroitin or glucosamine sulfates within thirty days before the Screening Visit.
- 9.3.2.19 The patient has grade III or IV osteoarthritis of either hip (Appendix G) by pelvic radiograph (radiograph required only if patient has symptoms of osteoarthritis of the hip in the opinion of the investigator).
- 9.3.2.20 The patient has undergone intraarticular corticosteroid injection into the knee joint under study within two months preceding the Screening Visit.
- 9.3.2.21 The patient has a diagnosis of fibromyalgia, bursitis, tendinitis, or neurological or vascular disease affecting the lower extremities.
- 9.3.2.22 The patient has ongoing treatment or expected treatment with any medication not allowed as described in Section 9.4.7.
- 9.3.2.23 The patient, in the opinion of the investigator, is unlikely to comply with the study protocol or is unsuitable for any other reason.

9.3.3 Removal of Patients from Therapy of Assessment

A patient may voluntarily terminate participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to terminate prematurely a patient's participation. The investigator must notify the clinical research associate (CRA) within 24 hours and document the reason for premature termination on the appropriate CRF.

Patients, whose participation is terminated prematurely after signing study consent but before study drug administration, will not require follow-up observations. Patients, whose participation is terminated prematurely after study drug administration, must undergo procedures normally performed at the Treatment Visit III (see Table 9.5a) within 7-10 days of termination from the study.

If, in the judgment of the investigator or Abbott Laboratories, continued exposure to a study drug represents a significant risk to patients, the study will be terminated.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

20

9.4 Treatments

9.4.1 Treatments Administered

Patients will be randomly assigned in an equal ratio to one of the following five treatment groups:

ABT-594 25 µg BID
ABT-594 50 µg BID
ABT-594 75 µg BID
Ibuprofen 400 mg TID
Placebo

ABT-594 and matching placebo will be supplied as soft elastic capsules (SEC).
Ibuprofen and matching placebo will be supplied as gelatin capsules. The 400 mg ibuprofen dose is provided as two 200 mg ibuprofen gelatin capsules.

Patients will receive two SEC (one capsule from Bottle A and one capsule from Bottle B) BID and two gelatin capsules (two capsules from Bottle C) TID for 22 days.

Table 9.4.1a Number and Type of Capsules by Treatment Regimen

Treatment Regimen	Number of Capsules Per Dose							
	Bottle A ¹ (BID)			Bottle B ¹ (BID)			Bottle C ² (TID)	
	25 µg ABT-594 SEC	50 µg ABT-594 SEC	Placebo ABT-594 SEC	25 µg ABT-594 SEC	50 µg ABT-594 SEC	Placebo ABT-594 SEC	200 mg Ibuprofen	Placebo Ibuprofen
ABT-594 25 µg	1	0	0	0	0	1	0	2
ABT-594 50 µg	0	0	1	0	1	0	0	2
ABT-594 75 µg	1	0	0	0	1	0	0	2
Ibuprofen 400 mg	0	0	1	0	0	1	2	0
Placebo	0	0	1	0	0	1	0	2

¹ Store at 36-46°F. Refrigerate.

² Store at room temperature and avoid excessive heat (104°F).

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

21

All patients will receive a supply of acetaminophen to be used as analgesic rescue medication. Acetaminophen will be supplied as Tylenol® 500 mg caplets. Patients may take up to two tablets each day of analgesic rescue medication and up to six caplets each week. In addition, patients will not be permitted to take analgesic rescue medication within 48 hours before the Baseline Visit and Treatment Visits I, II and III.

9.4.2 Identity of Investigational Products

Table 9.4.2a Identity of Investigational Products

Test Preparation Drug Product	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 25 µg SEC	39-904-AR-R1	27-335-YS-00	R.P. Scherer ¹
ABT-594 50 µg SEC	39-905-AR-R1	27-335-YS-00	R.P. Scherer ¹
ABT-594 placebo SEC	39-903-AR-R1	N/A	R.P. Scherer ¹
Ibuprofen 200 mg gelatin capsule ²	31-782-AR-03	N/A	Abbott ³
Ibuprofen placebo gelatin capsule	40-913-AR-AA	N/A	Applied Analytic Industries ⁴
Acetaminophen 500 mg caplet	TBD	N/A	McNeil Consumer ⁵

¹ St. Petersburg, FL

² Motrin® IB Caplet, 200 mg. Pharmacia & Upjohn Co., Lot 56BJW, encapsulated in Iron Gray Opaque No. 00 gelatin capsule.

³ Abbott Park, IL

⁴ Wilmington, NC

⁵ Ft. Washington, PA

ABT-594 25 µg SEC, 50 µg SEC and placebo SEC are identical in appearance.

Blinded ibuprofen 200 mg capsules will be prepared by encapsulating a Motrin® IB 200 mg caplet (Pharmacia & Upjohn Co.) in an Iron Gray Opaque No. 00 size gelatin capsule (identical to the placebo capsule) in order to keep the study drug appropriately blinded. In a study conducted by Abbott Laboratories, the dissolution performance of Motrin® IB 200 mg caplets and encapsulated (blinded) Motrin® IB 200 mg capsules

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 5

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

22

was compared. Blinding of ibuprofen caplets causes a slight slowing of dissolution. Testing at 120 minutes indicates that drug is completely released from the blinded product. All materials met the dissolution specification and blinded caplets are acceptable for clinical use.

9.4.2.1 Packaging and Labeling

Open label acetaminophen 500 mg caplets (analgesic rescue medication) will be packaged in bottles containing 100 caplets each. One bottle will be provided to each patient at the Screening Visit.

Each bottle of acetaminophen 500 mg caplets (Tylenol® Extra-Strength) will be labeled with a single-panel label that has been pre-printed with the study number, Abbott address, New Product Research Order (NPRO) number, lot number, contents, directions for use and storage conditions. Space will be provided on the label to record the patient's initials, birth year, and date dispensed.

Study drug supplies containing ABT-594 or matching placebo SEC and ibuprofen gelatin capsules or matching placebo will be blinded and packaged in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). ABT-594 SEC and matching placebo will be packaged in bottles containing 20 capsules each. Ibuprofen gelatin capsules and matching placebo will be packaged in bottles containing 60 capsules each. Three bottles, one containing 60 gelatin capsules and two each containing 20 soft elastic capsules, will be provided to each patient at the Baseline Visit and Treatment Visits I and II.

Each bottle of blinded study medication will be labeled with a single-panel blinded label that has been pre-printed with the study number, patient number, Abbott address, New Product Research Order (NPRO) number, contents, directions for use and storage conditions. Space will be provided on the label to record the patient initials and date dispensed.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

23

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies must be stored in a secure location until dispensed to a patient or until returned to Abbott Laboratories. ABT-594 study supplies (bottles containing SEC) must be refrigerated (36-46°F). Patients will be instructed to take the drug as prescribed and return the bottle to refrigeration as soon as possible. Ibuprofen drug supplies (bottles containing gelatin capsules) must be stored at room temperature and avoid excessive heat (104°F). Acetaminophen 500 mg caplet must be stored at room temperature, at controlled conditions.

9.4.2.3 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. Study drug will be dispensed in numerical order to each patient, who meets the enrollment criteria, by the investigator according to the patient numbers provided to each site (Section 9.4.3). The investigator or designee will record the patient number, patient initials and date dispensed to the patient on the Drug Accountability Form (Appendix E). The amount of study drug and analgesic rescue medication remaining will be recorded at the Baseline Visit (analgesic rescue medication only) and Treatment Visits I, II and III for each patient on the site Drug Accountability Form. An accurate running inventory of study drug will be kept and will include the NPRO number, CSI number(s), the number of capsules dispensed and the date study drug was dispensed for each patient. An overall accountability of the study medication will be performed and verified by the CRA throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for and returned to Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with the instructions of the CRA, will also be included in the shipment. The investigator agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

24

9.4.3 Method of Assigning Patients to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by the Department of Clinical Statistics at Abbott Laboratories. Approximately 250 patients will be randomized in an equal ratio to receive either ABT-594 25 µg BID, ABT-594 50 µg BID, ABT-594 75 µg BID, Ibuprofen 400 mg TID or placebo. After meeting entry criteria on Day 1, patients will be assigned randomization numbers in ascending numerical sequence per investigator site as they are enrolled in the study.

9.4.4 Selection of Doses in the Study

ABT-594 doses (25 µg, 50 µg, 75 µg) were selected on the basis of Phase I tolerability studies and represent doses below the maximally tolerated dose. No human data exist to indicate ABT-594 doses that are efficacious in the relief of pain.

The ibuprofen dose (400 mg TID) was selected using the approved labeling for the relief of the signs and symptoms of osteoarthritis.

The analgesic rescue medication dose (Section 9.4.1) was selected using the approved labeling for the relief of the minor pain of arthritis. In addition, analgesic rescue medication use is limited in order to differentiate the efficacy of ABT-594, ibuprofen and placebo.

9.4.5 Selection and Timing of Dose for Each Patient

Patients will be assigned randomly to treatment groups as described in Section 9.4.3. Patients will take BID doses of ABT-594 25, 50 or 75 µg or ABT-594 placebo within 30 minutes following breakfast and dinner (e.g., 7 AM and 7 PM). Patients will take TID doses of ibuprofen 400 mg or ibuprofen placebo immediately after a snack or meal (e.g., 7 AM, 1 PM, and 7 PM). All study drugs should be taken with at least one cup of water (240 cc).

No human data exist to indicate ABT-594 dosing frequencies that are efficacious in the relief in pain. The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. Ibuprofen dosing frequency was selected using the approved label.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

25

The analgesic rescue medication dosing frequency (Section 9.4.1) was selected using the approved labeling for the relief of the minor pain of arthritis. In addition, analgesic rescue medication use is limited in order to differentiate the efficacy of ABT-594, ibuprofen and placebo.

9.4.6 Blinding

Both the investigator and the patient will remain blinded to the patient's treatment throughout the course of the study. A label, which contains drug assignment, will be provided to the investigator in a separate sealed envelope for each patient. The sealed envelope will be retained by the study coordinator as part of the case report form. The study blind envelope may be broken if, in the opinion of the investigator, it is in the patient's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) **MUST** be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. The sponsor must then be notified within 48 hours of the blind being broken. The date, time, and reason for blind breakage must be recorded on the appropriate case report form.

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications, used over the prior two weeks, will be taken.

Patients who have taken chondroitin or glucosamine sulfates within 30 days of randomization will not be eligible for the study. Patients will not be allowed to take chondroitin or glucosamine sulfates during the study.

Patients who have received a hyaluronic acid injection within one year of randomization will not be eligible for the study. Patients will not be allowed to receive a hyaluronic acid injection during the study.

If the administration of any concurrent medication is necessary during the course of this study, the medication name, dosage information, frequency, dates of administration, and indication for use must be reported on the case report form.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

26

Concomitant analgesics (prescription or over-the-counter [OTC]), other than rescue analgesic medication (acetaminophen) or aspirin 81 mg daily (maximum), will not be allowed. Patients may not take acetaminophen more than one gram in any individual day or more than three grams in each of the three weeks of the Treatment Phase. Patients, however, will not be allowed to take analgesic rescue medication within 48 hours prior to the Baseline Visit and Treatment Visits I, II and III. Patients will record the time and dose of acetaminophen taken in their study diaries.

Aspirin, 81 mg daily maximum, is permitted. Patients taking higher doses may be switched to 81 mg daily prior to the Pre-Treatment Phase if the change in dose does not alter the efficacy of the aspirin treatment for the indication for which it was prescribed (in the opinion of the investigator in consultation with the prescribing physician, if any). Patients, who take aspirin during the study, must remain on a stable daily dose of aspirin throughout the Pretreatment and Treatment Phases of the study.

Patients may not undergo intraarticular corticosteroid injection or any surgical procedure to either knee during the study.

Physical therapy will be considered as a concomitant therapy. Patients may be enrolled as long as their physical therapy has been constant for two months prior to randomization. Patients are not allowed to start new physical therapy or to change significantly (in the opinion of the investigator) their physical therapy during this study.

Because of the potential interaction with ibuprofen, patients will not be allowed to take warfarin, corticosteroids, methotrexate or lithium.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, patients will be instructed to return all medication containers (even if empty) to the study coordinator at Treatment Visits I, II and III. Compliance with each study medication (including acetaminophen) will be documented by the study coordinator on the appropriate CRF.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

27

9.5 Efficacy, Pharmacokinetics and Safety Variables and Other Study Procedures

9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Study procedures will be performed as summarized in Table 9.5a, Study Procedures Flow Chart.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

28

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase		Pre-Treatment Phase		Treatment Phase				Post-Treatment Phase	
	Screening Visit	Between D-21 and D-7	Washout Period	Baseline Pain Assessment Period	Baseline Visit	Treatment Visit			D22 to D32	Follow-up Visit
						D8	D15	D22		
Informed Consent	X		D-6 to D-4	D-3 to D-1	D1 to D22	I	II	III ^a	D29 to D32	
Medical History	X				X ^b					
Physical Exam	X				X			X		X
Vital Signs	X ^c				X	X	X	X		X
ECG	X				X			X		X ^d
Clinical Laboratory Tests ^e	X				X	X	X	X		X ^d
Viral Hepatitis Screen	X									
Urine Drug and Alcohol Screen	X									
Pregnancy Test	X				X	X	X	X		
Radiographs	X ^f									
Collection and Processing of Blood Samples for ABT-594 Plasma Assay						X	X	X		
Genetic Polymorphism Sample					X					
Diary Issued	X				X	X	X	X		
Diary Collected					X	X	X	X		
Diary - Based Efficacy Measurements ^g				X	X ^{h,i}					
Site - Based Efficacy Measurements ^j					X	X	X	X		
Analgesic Rescue Medication Use Monitoring					X	X	X	X		
Patient Global Evaluation								X		
Dispense Analgesic Rescue Medication	X									

^a Or upon premature termination.

^b Interim history.

^c Includes orthostatic measurements at Screening Visit only.

^d Performed only if there are clinically significant abnormalities at the previous evaluation.

^e Chemistry, hematology and urinalysis.

^f Anytime within six months prior to Screening Visit.

^g Daily Pain Intensity Categorical Scale and VAS.

^h To be completed approximately 9 PM, two hours after evening dose.

ⁱ Except Day 22.

^j Pain Intensity Categorical Scale and VAS (each at rest and after walking) and WOMAC.

^k See Section 9.5.1.2.1.

^l Analgesic rescue medication only.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

29

Table 9.5a Study Procedures Flow Chart (Continued)

Study Activity	Screening Phase		Pre-Treatment Phase		Treatment Phase				Post-Treatment Phase	
	Screening Visit	Between D-21 and D-7	Washout Period	Baseline Pain Assessment Period	D1 to D22	Baseline Visit			Treatment Visit	Follow-up Visit
						D1	D8 I	D15 II	D22 III ^a	
Randomize Patient			D-6 to D-4	D-3 to D-1		X				D23 to D32
Dispense Study Drug						X	X	X		
Adverse Event Monitoring ^k						X	X	X	X	X
Concomitant Medication Monitoring						X	X	X	X	X
Study Drug Accountability						X ^l	X	X	X	

^a Or upon premature termination.

^b Interim history.

^c Includes orthostatic measurements at Screening Visit only.

^d Performed only if there are clinically significant abnormalities at the previous evaluation.

^e Chemistry, hematology and urinalysis.

^f Anytime within six months prior to Screening Visit.

^g Daily Pain Intensity Categorical Scale and VAS.

^h To be completed approximately 9 PM, two hours after evening dose.

ⁱ Except Day 22.

^j Pain Intensity Categorical Scale and VAS (each at rest and after walking) and WOMAC.

^k See Section 9.5.1.2.1.

^l Analgesic rescue medication only.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 6

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

30

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer will instruct the patient on how to record analgesic rescue medication use in the diary, and how to perform diary-based and site-based assessments.

Diary-based assessments include the four-point Daily Pain Intensity Categorical Scale and the Daily Pain Intensity VAS. Each patient will receive four diaries over the course of the study. The first diary will be issued at the Screening Visit and collected at the Baseline Visit, the second will be issued at the Baseline Visit and collected at Treatment Visit I, the third will be issued at Treatment Visit I and collected at Treatment Visit II and the fourth will be issued at Treatment Visit II and collected at Treatment Visit III. Diaries will be retained at the investigative site and considered source documents. Information from the diaries will be transferred onto the appropriate CRF.

Site-based assessments include the four-point Pain Intensity Categorical Scale, the Pain Intensity VAS, the WOMAC and the Patient Global Evaluation (the latter only at the Follow-up Visit).

All efficacy measurements of the knee will refer to the knee under study.

Daily Pain Intensity Categorical Scale and Daily Pain Intensity VAS

Patients will assess Pain Intensity by completing a four-point categorical scale and marking a VAS (Appendix F) in their diaries. These assessments will be completed at the same time each evening (approximately 9 PM), two hours after the evening dose of study medication. Patients will record the time they completed these assessments.

Pain Intensity Categorical Scale and Pain Intensity VAS at Rest

At the investigation site, patients will assess Pain Intensity at rest by completing a four-point categorical scale and marking a VAS (Appendix F). These assessments will be completed at the Baseline Visit and at Treatment Visits I, II and III. The time these assessments were performed and the time and date of patients' prior two doses of study drug will be recorded.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

31

Pain Intensity Categorical Scale and Pain Intensity VAS after Walking

At the investigation site, patients will assess Pain Intensity after walking 50 feet by completing a four-point categorical scale and marking a VAS (Appendix F). These assessments will be completed at the Baseline Visit and at Treatment Visits I, II and III. The time these assessments were performed and the time of patients' prior two doses of study drug will be recorded.

WOMAC Index Version VA 3.0

The WOMAC Index (Appendix H) will be completed by patients at the Baseline Visit and at Treatment Visits I, II and III. The WOMAC Index, completed at the Baseline Visit, will serve as the baseline. A user's guide for the WOMAC Index will be provided to the investigator.

Rescue Medication Use

Patients will record their use of analgesic rescue medication (acetaminophen) during the Pre-Treatment and Treatment Phases (Day -6 to Day 22). Patients will record in their diaries the date and time of use and the dose of acetaminophen taken.

Patient Global Evaluation

The Patient Global Evaluation (Appendix F) of analgesic relief due to study drug will be performed at Treatment Visit III (Day 22) or upon premature termination.

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative will explain the nature of the study to the patient and answer all questions regarding this study. Prior to any screening procedures being performed on the patient, the informed consent statement will be reviewed and signed and dated by the patient and the person who administered the informed consent. A copy of the informed consent form will be given to the patient

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

32

and a copy will be placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the patient received a signed copy.

Medical History

A complete medical history will be obtained from each patient during the Screening Visit. In addition, history of nicotine use and medication (prescription or OTC) use over the two weeks prior to screening will be recorded. The medical history will be updated at the Baseline Visit (Day 1).

Physical Examination

A physical examination, including weight, will be performed at the Screening Visit, Baseline Visit (Day 1), Treatment Visit III (Day 22) and at the Follow-up Visit (Between Day 29 and Day 32). Height will be obtained at the Baseline Visit only. The physical examination performed at the Baseline Visit will serve as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate, respiration rate, and oral temperature will be measured at the Screening Visit, Baseline Visit (Day 1), Treatment Visits I, II and III (Day 8, 15 and 22) and at the Follow-up Visit (between Day 29 and Day 32). Orthostatic blood pressure will be measured at the Screening Visit. Vital sign measurements at the Baseline Visit will serve as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) should be obtained after the patient has been sitting for at least three minutes. Orthostatic measurements should be obtained after three minutes in the supine position and then after one minute in the standing position. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Patients should not wear tight sleeves. Ideally, the patient's blood pressure should be measured in the same arm by the same study personnel using the same instrument..

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

33

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws. Patients should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

Electrocardiogram (ECG)

A 12-lead ECG will be obtained at the Screening Visit, Baseline Visit (Day 1) and Treatment Visit III (Day 22). An ECG will be performed at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The ECG performed at the Baseline Visit will serve as the baseline ECG.

A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples will be obtained for the laboratory tests listed in Table 9.5b at the Screening Visit, Baseline Visit (Day 1), and Treatment Visits I, II and III (Day 8, 15 and 22). Laboratory tests will be obtained at the Follow-up Visit if clinically significant abnormalities are present on the previous evaluation. The laboratory test results obtained at the Baseline Visit will serve as the baseline results. Blood draws should be performed after any pain assessments or vital sign determinations during a visit.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

34

Table 9.5b Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
RBC count	Total bilirubin	pH
WBC count	Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)	Bilirubin
Neutrophils	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Lymphocytes	Chloride	
Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)	Calcium	
Platelet count (estimate not acceptable)	Inorganic phosphorus	
Prothrombin Time (PT)	Uric Acid	
Partial Thromboplastin Time (PTT)	Bicarbonate	
	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

In addition, a creatinine clearance will be calculated based upon clinical laboratory tests at the Screening Visit according to the following formula:

$$\text{MEN: CrCl (mL/min)} = \frac{\text{Ideal Body Weight (kg)} \times (140 - \text{age in yrs})}{72 \times \text{serum creatinine (mg/dl)}}$$

$$\text{Ideal Body Weight (men) in kg} = 50 + (2.3 \times \text{height in inches over 5 ft})$$

WOMEN: 0.85 x value calculated for men

$$\text{Ideal Body Weight (women) in kg} = 45.5 + (2.3 \times \text{height in inches over 5 ft})$$

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

35

Certified laboratories will be utilized to process and provide results for the clinical laboratory tests.

The investigator will review all laboratory test results. For each abnormal result, the investigator will assess clinical significance and provide an etiology, if clinically significant. The assessment of etiology will use one of the following categories:

- Concurrent Medication (medication must be specified)
- Concurrent Disease (disease must be specified)
- Sample or laboratory error
- Unknown
- Non-fasting specimen (chemistry only)
- Other (must specify)

All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A copy of each laboratory report must be included with the case report form.

Viral Hepatitis Screen

Patients will undergo serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody) at the Screening Visit. The hepatitis test panel will be performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens will be tested for drugs of abuse and alcohol at the Screening Visit and will be performed by the central laboratory.

Pregnancy Test

A urine pregnancy test will be performed by designated study personnel at the Screening Visit, Baseline Visit and at Treatment Visits I, II and III. A lactating or pregnant female will not be eligible for participation in this study.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

36

Radiographs

Weight-bearing anteroposterior radiographic views of the knee under study and the pelvis (if the patient is symptomatic of osteoarthritis of either hip) must be taken at the Screening Visit if not already performed within the 6 months prior to the Screening Visit. Radiographs must be reviewed by a board certified rheumatologist or a radiologist who is experienced in bone and joint radiography. Radiographs will be assessed using the Osteoarthritis Severity Grades for Knee and Hip Joints (see Appendix G).

9.5.1.2.1 Adverse Events

An adverse event is defined as any unexpected and unfavorable event such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of a drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the patient.

The patient will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken and all adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the patient, will be reported on the appropriate CRF.

The investigator will assess and record any adverse event in detail on the adverse event CRF including the date and time of onset, description, severity, intermittence, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as intermittent or continuous, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

37

Table 9.5c Definitions for Investigator Rating of Adverse Event Severity

Rating	Definition
Mild	The adverse event is transient and easily tolerated by the patient.
Moderate	The adverse event causes the subject discomfort and interrupts the patient's usual activities.
Severe	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Rating	Definition
Probable	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possible	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 7

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

38

Adverse events will be monitored continuously from the time of study drug administration to the Follow-Up Visit. Only serious adverse events will be collected from the time of informed consent to study drug administration. Patients will be instructed to report to the investigator any other adverse events that occur after the Follow-up Visit.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

Since measurements of pain intensity are efficacy measurements in this study, any change in pain intensity due to the underlying pain state under study will not be considered adverse events for the purposes of this study.

9.5.1.2.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to Abbott as a serious adverse event within 24 hours of occurrence or notification to the site:

- | | |
|-------------------|--|
| Fatal: | An event which results in the death of a patient. |
| Life-Threatening: | An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| Hospitalization: | An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility. |

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

39

Prolongs Hospitalization:	An event which occurs while the study patient is hospitalized and that prolongs the patient's hospital stay.
Persistent or Significant Disability:	An event which results in a condition that interferes with the activities of daily living of a study patient (e.g., permanent loss of vision).
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Requires Medical or Surgical Intervention:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, spontaneous and elective abortions will be reported to Abbott Laboratories as serious adverse events.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone, one of the following people at Abbott Laboratories within 24 hours of being made aware of any serious adverse event (SAE).

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

40

Bruce G. McCarthy, M.D.
Associate Medical Director
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-3537
Office: (847) 935-6244
Home: (773) 529-5729
Fax: (847) 938-5258

Christopher J. Silber, M.D.
Venture Head
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-3537
Office: (847) 938-5236
Home: (847) 615-0428
Fax: (847) 938-5258

Marilyn Collicott
Senior Clinical Research Associate
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-3537
Office: (847) 938-1199
Home: (414) 529-3282
Fax: (847) 938-5258

In addition, a written confirmation of the occurrence, including any supplementary data, must be sent within three days of the telephone report to:

Bruce G. McCarthy, M.D.
Dept. 48Q, Bldg. AP34
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-3537
Fax: (847) 938-5258

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study are standard and validated. All clinical and laboratory procedures in this study are standard and generally accepted.

9.5.3 Efficacy Variables

All efficacy variables will be derived from the efficacy measurements (Section 9.5.1.1).

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

41

9.5.3.1 Primary Variable

The primary efficacy variable in the study will be the change from baseline of the average Daily Pain Intensity Categorical Scale score from each patient's diary to the corresponding average of the last three days on study drug.

9.5.3.2 Secondary Variables

The secondary efficacy variables include the change from baseline of the average Daily Pain Intensity VAS score from each patient's diary to the corresponding average of the last three days on the study drug, change from baseline of the pain intensity scores (categorical and VAS scores at rest and after walking 50 feet) at each visit, change from baseline to the total and three subscales of the WOMAC Index (pain, stiffness, and physical function) at each visit, the patient global Evaluation at Visit III, and average daily dose of and percent of days using analgesic rescue medication. The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site.

9.5.4 Drug Concentration Measurements

9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay

Blood samples for ABT-594 plasma assay will be collected for all patients at Treatment Visits I, II and III. The time and date of the most recent dose of SEC will be recorded in the CRF. One blood sample (approximately 7 mL) will be collected into a sodium heparin evacuated collection tube at each visit. Blood draws should be performed after any pain assessments or vital sign determinations during a visit.

All blood samples will be immediately stored at 4°C or below. The samples will be separated by centrifugation within one hour after sample collection. The supernatant will be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, patient number, initials, and date and time of sample collection. This information will also

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

42

be recorded on the appropriate CRF. All labeled plastic vials will be placed in a rack to prevent breakage. **Plasma samples for determination of ABT-594 must be frozen at -5°C or colder within one hour from centrifugation.** All specimens will be kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

9.5.4.2 Shipment of Plasma Samples

An inventory list of the samples included in the shipment must accompany the shipment. The inventory list will include the shipping date, number of samples in the container, drug identification, Abbott protocol number, patient numbers, sample type, sampling times, and missing samples. The frozen samples will be packed in dry ice sufficient to last two days during shipping.

Arrangements will be made with Abbott Laboratories for shipping of the plasma samples to the following Abbott address:

Sample Receiving
Abbott Laboratories
Dept. 4TA, Bldg. AP9
100 Abbott Park Road
Abbott Park, IL 60064-3537
Phone: (847) 937-0889
Fax: (847) 938-9898

On the day of shipping, a copy of the inventory sheet should be faxed to the Sample Receiving Department at (847) 938-9898.

9.5.5 Blood Samples for Genetic Polymorphism Analysis

Two (2) 10 ml whole blood samples will be collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

43

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis will not be reported with the study summary. The samples may also be used for development of a diagnostic test for drug response.

The pharmacogenetic analyses involve two methods: one which examines known genes believed to be involved in the particular response (Candidate Gene), and one which uses a high density marker map to locate and identify genes related to the response (Genomic Association) by comparing the marker profile between the patients with an effect and a corresponding negative control group. The Candidate Gene method includes genes related to drug metabolism, drug targets or target pathways, and others including genes relating to cellular homeostasis. The Genomic Association method utilizes a map of single nucleotide polymorphisms which by themselves are essentially meaningless, but when correlated with groups of two distinct patient groups allow the identification of the gene(s) related to the difference between the groups. For the purpose of pharmacogenetic studies such as this, the difference would be related to the response to the drug or the presence or absence of the disease being tested.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting will entail a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and be given a CRF completion workbook for reference. The CRAs will monitor each site approximately every 2 to 4 weeks. At each visit, 100% source-document review will be made against the entries on the CRFs and a quality-assurance

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

44

check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All CRFs must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the CRFs for completeness and accuracy and sign and date the set of case report forms where indicated. CRFs will be reviewed periodically for completeness, legibility, and acceptability by Abbott Laboratories personnel (or their designee) and the investigator (or designee) at the study site. The investigator must agree to provide Abbott (or designee) access to all source documents in order to verify CRF entries.

Data captured on the CRF will be entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF will be reviewed and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values, and any necessary corrections will be made to the database and documented via addenda or audit trail.

The laboratory results will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests will be two-tailed and considered statistically significant if the p-value (type one error rate) is less than or equal to 0.05 (when rounded to three decimal places).

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

45

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group, along with an assessment of ABT-594 linear dose response. No comparison will be made between ABT-594 and ibuprofen. Appropriate secondary comparisons will be made as considered necessary.

Baseline value for all variables is defined as the last value obtained prior to receiving study drug.

9.7.1.1 Data Sets Analyzed

Efficacy analyses will be performed for two sets of data: intent-to-treat patients and evaluable patients, as defined in accordance with Sections 9.3.1 and 9.3.2. Patients receiving at least one dose of study drug with at least one baseline and one post-dose pain assessment will be included in the intent-to-treat analyses. Classification of patients regarding acceptability of data for evaluable efficacy analyses will be carried out by the project team (clinical, data management, and statistics) prior to their knowledge of double-blind treatment assignment. Safety analyses will be performed with all randomized patients who receive at least one dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the treatment groups. Comparability among the treatment groups will be assessed by a one-way analysis of variance (ANOVA), with treatment group as the main effect for quantitative variables, and by Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

The primary efficacy variable in the study will be the change from baseline of the average Daily Pain Intensity Categorical Scale score from each patient's diary to the corresponding average of the last three days on study drug. The baseline pain score for diary data is defined as the average of the last three days of pain scores prior to dosing.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 8

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

46

The secondary efficacy variables include the change from baseline of the average Daily Pain Intensity VAS score from each patient's diary to the corresponding average of the last three days on the study drug, change from baseline of the pain intensity scores (categorical and VAS scores at rest and after walking 50 feet) at each visit, change from baseline to the total and three subscales of the WOMAC Index (pain, stiffness, and physical function) at each visit, the patient global Evaluation at Visit III, and average daily dose of and percent of days using analgesic rescue medication. The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site. Change to intermediate time points will also be examined.

The change from baseline pain scores and average daily dose and percent of days using analgesic rescue medication will be analyzed by using analysis of variance (ANOVA) techniques with the effects of treatment, investigator sites and the interaction between the treatment and investigator sites. Investigator sites with few patients may be combined based on geographical location prior to breaking the blind.

If indicated, exploratory analyses will be performed on the change from baseline efficacy pain scores, such as analysis of covariance (ANCOVA), with baseline pain score as a covariate. If the change from baseline pain scores do not follow a normal distribution then the nonparametric Friedman's test will be applied.

Dose response for ABT-594 will be explored using both a parametric regression model and nonparametric tests, with placebo included and without placebo. If the effect of investigator sites is not significant then the nonparametric Jonckheere-Terpstra test will be used instead of Page's test to assess dose response of ABT-594.

The final global evaluation score will be compared among the treatment groups by Cochran-Mantel-Haenszel test controlling for investigative site.

Other analyses will be performed as appropriate .

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

47

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, will be performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses will use the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every patient in the analysis will have data for each specified evaluation. This technique reduces the bias caused by patients who prematurely terminate for lack of efficacy. The "observed cases" (OC) analysis will not estimate the missing evaluation, and a patient who does not have pain evaluation on a scheduled visit or day will be excluded from the OC analysis for that visit or day.

9.7.1.4 ABT-594 Plasma Assay

The relationship between ABT-594 plasma concentration and efficacy parameters may be explored.

9.7.1.5 Safety

All patients receiving at least one dose of study drug will be evaluated for safety.

Adverse events will be coded using the COSTART V⁵ dictionary. Treatment-emergent adverse events (i.e., those which begin or worsen in severity after randomized study drug is taken) will be tabulated by body system and COSTART term for each treatment group. Pairwise comparisons between treatment groups will be made using Fisher's exact test for the proportion of patients reporting a particular adverse event. Analyses by subgroup will be performed as appropriate.

Laboratory data will be analyzed using a one-way ANOVA with treatment as the main effect. Baseline comparability among treatment groups will be assessed by the overall F-test of the one-way ANOVA. The primary analyses will be on the change from baseline to the final values during the study for each laboratory variable.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

48

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory results which satisfy the criteria for potentially clinically significant results (Appendix I) will be identified.

Mean changes from baseline to the final values for both vital signs and ECG will be analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfy the criteria for potentially clinically significant results (Appendix I) will be identified.

Additional safety analyses will be performed as indicated.

9.7.2 Determination of Sample Size

The study is designed to enroll approximately 250 patients (approximately 50 patients in each treatment group). This sample size allows for the detection of a 20% difference in the percentage of patients experiencing improvement between ABT-594 and placebo at 0.05 two-tailed type I error with approximately 56% power. It is expected that 25% of placebo patients and 45% of ibuprofen patients will experience improvement on the global evaluation.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

This study will be conducted in accordance with the protocol, GCP, all applicable local, state federal regulations and regulatory requirements. Neither the investigator nor the CRO will modify this protocol without first obtaining the concurrence of Abbott Laboratories. The modification must be documented in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the patient or those of an administrative or clarifying nature, must be reviewed and approved by the Institutional Review Board before implementation. Abbott Laboratories must submit protocol amendments to the FDA and possibly to other government agencies.

This study will be terminated if these conditions are not met.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

49

10.0 Protocol Deviations

When deviation from the protocol is deemed necessary for an individual patient, the investigator or other physician in attendance must contact the site study monitor at the CRO, who will contact Abbott Laboratories. Such contact will be made as soon as possible to permit a decision as to whether or not the patient is to continue in the study. Any departures from the protocol will be authorized only for that one patient. A description of the departure from the protocol and the reason for it will be recorded on the CRF.

11.0 Use of Information and Publication

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 90 days before the date of submission to the intended publisher.

Neither the subject nor their physician will be informed of individual patient pharmacogenetic results, should they be performed, nor will anyone not directly involved in this research. This is due to the fact that, 1) the patient and their physician are already

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

50

aware of the patient's particular response to the drug and the study information would not affect their future medical care, and 2) if an association is established between a genetic sequence and a treatment response, separate studies must be conducted in order to validate or confirm the results and the properties of the test prior to the necessary regulatory approval to use the test for diagnostic purposes. DNA samples from this protocol may be used either for gene identification, validation, or diagnostic test development studies, as well as discovery of genes related to primary osteoarthritis and pain associated with osteoarthritis.

12.0 Completion of The Study

The investigator will complete and report this study in satisfactory compliance with the protocol within nine months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon in writing by both the investigator and Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are not pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

IN/R-S/1/ABT594/98826/98826AM2/P30-52
G02Q143010

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

51

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

52

14.0 References

1. American Academy of Pain Medicine (1997). The Use of Opioids for the Treatment of the Treatment of Chronic Pain. Pp. 1-4.
2. Twycross R. Pain Relief in Advanced Cancer. Churchill Livingstone, Endinburgh, 1994.
3. Sullivan JP and Bannon AW. Epibatidine: pharmacologic properties of a novel nicotinic acetylcholine agonist and analgesic agent. *CNS Drug Rev.* 2(1):21-39, 1996.
4. Sullivan JP, Briggs CA, Donnelly-Roberts D, Brioni JD, Radek RJ, McKenna DG, Campbell JE, Arneric SP, Decler MW, Bannon AW. (+)-Epibatidine can differentially evoke responses mediated by putative subtypes of nicotinic acetylcholine receptors (nAChRs). *Med Chem Res*, 4:502-516; 1994.
5. "COSTART" Coding Symbols for Thesaurus of Adverse Reaction Terms: Third Edition, Department of Health and Human Services, Food and Drug Administration, Rockville, MD, 1989.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

53

Appendix A

Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott Laboratories has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed protocol for the study.
2. A signed Form FDA 1572 or equivalent document certifying the investigator's agreement to comply with U.S. Federal (21 CFR, ICH GCP Guidelines) regulations governing the conduct of the study.
3. A current curriculum vitae of the investigator. If sub-investigators will participate in the study, a curriculum vitae for each.
4. Requirements for the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
 - A copy of the letter of approval of the IRB/IEC. The letter must specify that both the protocol and consent form were approved.
 - The names and affiliations of the members of the IRB/IEC or assurance number.
 - If the principal and/or sub-investigator is a member of the IRB/IEC, a letter stating that he/she did not participate in the review or approval of the protocol or consent form.
5. A specimen copy of the IRB/IEC-approved informed consent document to be used in the study.
6. A list of normal ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

As a rule, these documents will be provided in the course of one or more visits to the investigator by an Abbott Laboratories representative. Usually the study cannot begin until all of the documents listed above have been provided.

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

54

Appendix B

Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,
35th World Medical Assembly, Venice, Italy, in October 1983 and
41st World Medical Assembly, Hong Kong, in September 1989.
48th General Assembly, Somerset West, Republic of South Africa 1996

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 9

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

55

Appendix B (Cont.)

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

56

Appendix B (Cont.)

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obligated to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.
10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

57

Appendix B (Cont.)

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician - patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REASON FOR REVISION: Revised to correspond to the amendment adopted by the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa 1996.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

58

Appendix C

Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott Laboratories are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is actually a form letter addressed to the sponsor (Abbott Laboratories), summarizing the investigators qualifications for the study and their willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. To secure prior approval of the study by an appropriate institutional review board which conforms to FDA regulations.
2. To make at least yearly reports on the progress of the study to the above committee, and a final report within three months of study completion.
3. To maintain current running records of the receipt, administration, and disposition of study medication and to return all unused study medication to Abbott Laboratories.
4. To obtain valid written informed consent from each patient who participates in the study.
5. To prepare and maintain adequate case histories of all persons entered into the study, including case report forms, hospital records, laboratory results, etc., and to maintain these data for a minimum of two years following notification by Abbott Laboratories that all investigations have been discontinued with this drug.
6. To identify all subinvestigators who will also supervise drug administration.
7. To report adverse effects to Abbott Laboratories promptly. In the event of serious or unexpected adverse event, to notify Abbott Laboratories immediately by telephone.
8. To allow possible inspection and copying by the FDA of case reports and records of drug distribution.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

59

Appendix D

Elements of the Consent Form

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

For IND Studies, procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all patients participating in PPD Clinical Research studies or the patients' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of patients involved in the trial.
4. The expected duration of the patient's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The patient's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the patient and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the patient for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the patient, this should be stated.

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

60

Appendix D (Cont.)

13. The anticipated prorated payment, if any, to the patient for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
15. A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research patient's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the patient.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the patients' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the patient or the patient's legally acceptable representative is authorizing such access.
21. A statement that the site will collect information on the patient per ICH requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency will also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site.
22. A statement that the records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the patients' participation in the trial may be terminated.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

61

Appendix D (Cont.)

24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the patient may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the consent is given to the patient.
29. The statement, "I agree to participate..."
30. A place for the patient or the patient's legally acceptable representative to sign and date.
31. A place for the person who conducted the informed consent discussion to sign and date.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-826

Incorporating Amendment Numbers One and Two - 12/22/98

62

Appendix E **Sample Abbott Laboratories Drug Accountability Form**

Date Received (M/D/Y)	Clinical Supplies Invoice No.	No. of Medication Containers Received
/ /		
/ /		

Study M98-826

NPRO #: _____

Investigator's Name: _____

Location: _____

Patient Number: _____

Patient Initials: _____

Visit	DISPENSED TO PATIENT			RETURNED FROM PATIENT			VERIFIED BY CRA	
	Bottle #	# Capsules or SEC	Date	By*	Date	No. of Capsules or SEC Remaining	By*	Date
Baseline	A	20						
	B	20						
	C	60						
Visit I	A	20						
	B	20						
	C	60						
Visit II	A	20						
	B	20						
	C	60						

* Pharmacist/Coordinator/Nurse

+ CRO monitor

CONFIDENTIAL INFORMATION **ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

63

Appendix F

Pain Assessments

The time and date of every pain assessment will be recorded.

The patient should be reminded that each assessment should be performed independently of previous assessments.

Daily Pain Intensity Categorical Scale

The patient's pain intensity will be assessed by completion of the following statement in the patient's diary.

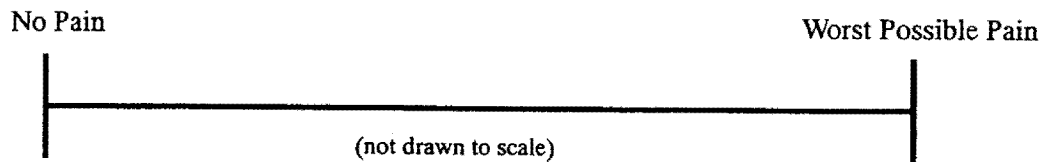
How severe was your osteoarthritis pain during the last 24 hours?

- | | |
|---|----------|
| 0 | None |
| 1 | Mild |
| 2 | Moderate |
| 3 | Severe |

Daily Pain Intensity Visual Analog Scale (VAS)

The patient will place a line on the VAS in the diary to indicate the magnitude of his/her pain.

How severe was your osteoarthritis pain during the last 24 hours?



Using a standard ruler supplied by Abbott, site personnel will measure the distance in millimeters (0-100 mm) from the left side of the scale to the patient's vertical mark and record this number on the appropriate CRF page.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

PART 10

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

64

Appendix F (Cont.)

Pain Intensity Categorical Scale at Rest and After Walking

The patient's pain intensity will be assessed by completion of the following statement.

My pain at this time is:

- 0 None
- 1 Mild
- 2 Moderate
- 3 Severe

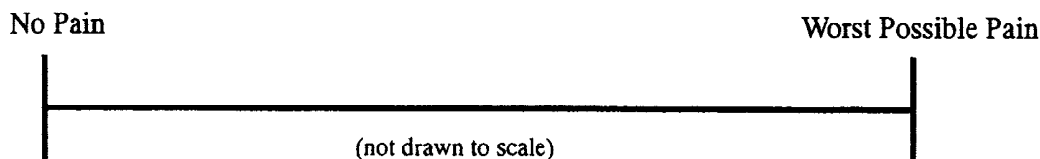
Patients will rate their Pain Intensity in the following two settings:

- After three minutes of sitting in a chair
- Immediately after walking 50 feet.

Pain Intensity VAS at Rest and After Walking

The patient will place a line on the VAS in the patient pain assessment worksheet to indicate the magnitude of his/her pain.

My pain at this time is:



Using a standard ruler, site personnel will measure the distance in millimeters (0-100 mm) from the left side of the scale to the patient's vertical mark and record this number on the appropriate CRF page.

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

65

Appendix F (Cont.)

Patients will rate their Pain Intensity in the following two settings:

- After three minutes of sitting in a chair
- Immediately after walking 50 feet.

Patient Global Evaluation

The patient's overall impression of the study drug will be assessed by completion of the following statement:

How would you rate the study medication?

- 4 Excellent
- 3 Good
- 2 Fair
- 1 Poor

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-826
Incorporating Amendment Numbers One and Two - 12/22/98

66

Appendix G
Osteoarthritis Severity Grades for Knee and Hip Joints Adapted from
the Council for International Organizations of Medical Sciences 1963

Knee

- Grade 0: Normal
- Grade I: Doubtful narrowing of joint space and possible osteophytic lipping.
- Grade II: Definite osteophytes and possible narrowing of joint space.
- Grade III: Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.
- Grade IV: Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

Hip Joints

- Grade 0: Normal
- Grade I: Possible narrowing of joint space medially and possible osteophytes around femoral head.
- Grade II: Definite narrowing of joint space inferiorly, definite osteophytes and slight sclerosis.
- Grade III: Marked narrowing of joint space, slight osteophytes, some sclerosis and cyst formation and deformity of femoral head and acetabulum.
- Grade IV: Gross loss of joint space with sclerosis and cysts, marked deformity of femoral head and acetabulum and large osteophytes.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.



6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

67

Appendix H

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Version VA3.0

INSTRUCTIONS TO PATIENTS	
<p>In Sections A, B, and C questions will be asked in the following format and you should give your answers by putting an "X" on the horizontal line.</p>	
<p>EXAMPLES:</p>	
<p>1. If you put your "X" at the left of the line as shown below, then you are indicating that you have no pain.</p>	
No Pain	
<p>2. If you put your "X" at the right end of the line as shown below, then you are indicating that your pain is extreme.</p>	
No Pain	
<p>3. Please note:</p> <ul style="list-style-type: none"> a) that the further to the right you place your "X" the more pain you are experiencing. b) that the further to the left you place your "X" the less pain you are experiencing. c) please do not place your "X" past the end of the line. 	
<p>You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.</p>	
<p>Think about your _____ (study joint) when answering the questionnaire. Indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your _____ (study joint).</p>	
<p>Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.</p>	

Copyright©1996 Nicholas Bellamy
 All Rights Reserved

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

68

Appendix H (Cont.)

WOMAC VA3.0 QUESTIONNAIRE

WOMAC

Section A

PAIN

Think about the pain you felt in your _____ (study joint)
 due to your arthritis during the last 48 hours.

(Please mark your answers with an "X".)

QUESTION: How much pain do you have?		Study Coordinator Use Only
1. Walking on a flat surface. No Pain ----- Extreme Pain		PAIN1 -----
2. Going up or down stairs. No Pain ----- Extreme Pain		PAIN2 -----
3. At night while in bed, i.e., pain that disturbs your sleep. No Pain ----- Extreme Pain		PAIN3 -----
4. Sitting or lying. No Pain ----- Extreme Pain		PAIN4 -----
5. Standing upright. No Pain ----- Extreme Pain		PAIN5 -----

Copyright©1998 Nicholas Bellamy
 All Rights Reserved

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

69

Appendix H (Cont.)

WOMAC VA3.0 QUESTIONNAIRE

WOM,

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your _____ (study joint) due to your arthritis during the last 48 hours.

Stiffness is a sensation of decreased ease in moving your joint.

(Please mark your answers with an "X".)

<p>6. How <u>severe</u> is your stiffness <u>after first awakening</u> in the morning?</p> <p>No Stiffness ----- Extreme Stiffness</p> <p>7. How <u>severe</u> is your stiffness after sitting, lying or resting <u>later in the day</u>?</p> <p>No Stiffness ----- Extreme Stiffness</p>	<p>Study Coordinator Use Only</p> <p>STIFF6 _____</p> <p>STIFF7 _____</p>
---	---

Copyright©1998 Nicholas Bellamy
 All Rights Reserved

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

70

Appendix H (Cont.)

WOMAC VA3.0 QUESTIONNAIRE

WOMC1-3

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean your ability to move around and to look after yourself. (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?		Study Coordinator Use Only
8. Descending stairs.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN8 _____
9. Ascending stairs.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN9 _____
10. Rising from sitting.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN10 _____
11. Standing.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN11 _____
12. Bending to the floor.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN12 _____
13. Walking on flat surface.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN13 _____

Copyright©1998 Nicholas Bellamy
 All Rights Reserved

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

71

Appendix H (Cont.)

WOMAC VA3.0 QUESTIONNAIRE

WOMc2-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean your ability to move around and to look after yourself. (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?		Study Coordinator Use Only
14. Getting in/out of car, or getting on or off a bus.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN14 _____
15. Going shopping.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN15 _____
16. Putting on your socks or stockings.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN16 _____
17. Rising from bed.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN17 _____
18. Taking off your socks or stockings.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN18 _____
19. Lying in bed.	<div> <div>No Difficulty</div> <div>Extreme Difficulty</div> </div>	PFTN19 _____

Copyright © 1998 Nicholas Bellamy
 All Rights Reserved

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 11

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

72

Appendix H (Cont.)

WOMAC VA3.0 QUESTIONNAIRE

WOMc3-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean your ability to move around and to look after yourself. (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?	Study Coordinator Use Only
20. Getting in or out of the bath. No Difficulty ----- Extreme Difficulty	PFTN20 _____
21. Sitting. No Difficulty ----- Extreme Difficulty	PFTN21 _____
22. Getting on or off the toilet. No Difficulty ----- Extreme Difficulty	PFTN22 _____
23. Performing heavy domestic duties. No Difficulty ----- Extreme Difficulty	PFTN23 _____
24. Performing light domestic duties. No Difficulty ----- Extreme Difficulty	PFTN24 _____

Copyright © 1996 Nicholas Bellamy
 All Rights Reserved

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

73

Appendix I
Potentially Clinically Significant Values for Laboratory
Determinations, Vital Signs and Electrocardiogram Variables

Hematology	Very Low	Very High
Hemoglobin (g/dL)		
Female	≤ 9.5	≥ 16.5
Male	≤ 11.5	≥ 18.5
Hematocrit (%)		
Female	≤ 32	≥ 50
Male	≤ 37	≥ 55
Red Blood Cells ($\times 10^{12}/L$)		
Female	≤ 3.5	≥ 6.0
Male	≤ 3.8	≥ 7.0
White Blood Cells ($\times 10^9/L$)	≤ 2.8	≥ 16.0
Platelet Count ($\times 10^9/L$)	≤ 75	≥ 700
Eosinophils (%)		≥ 10
Basophils (%)		≥ 10
Lymphocytes (%)		≥ 75
Monocytes (%)		≥ 15
Neutrophils (%)	≤ 15	
Bands (%)		≥ 10
Mean Corpuscular Volume (fL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Mean Corpuscular Hemoglobin Concentration (g/dL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Atypical Lymphocytes (%)		≥ 5
Prothrombin Time (sec)		$\geq 2 \text{ ULN}$
Partial Thromboplastin Time (sec)		$\geq 2 \text{ ULN}$

LLN = Lower limit of normal ULN = Upper limit of normal

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES
 No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

74

Appendix I (Cont.)

Chemistry	Very Low	Very High
Albumin (g/dL)	≤ 2.5	
Alkaline Phosphatase (IU/L)		$\geq 3 \times \text{ULN}$
Bicarbonate (mEq/L)	≤ 12	≥ 38
BUN (mg/dL)		≥ 30
Calcium (mg/dL)	≤ 8.2	≥ 12
Chloride (mEq/L)	≤ 90	≥ 118
Cholesterol (mg/dL)		≥ 600
Creatinine (mg/dL)		≥ 2.0
Direct Bilirubin (mg/dL)		≥ 2.0
Glucose (mg/dL)	≤ 45	≥ 175
LDH (IU/L)		$\geq 3 \times \text{ULN}$
Inorganic Phosphorus (mg/dL)	≤ 1.7	≥ 5.5
Potassium (mEq/L)	≤ 3.0	≥ 6.0
SGOT/AST (IU/L)		$\geq 3 \times \text{ULN}$
SGPT/ALT (IU/L)		$\geq 3 \times \text{ULN}$
Sodium (mEq/L)	≤ 126	≥ 156
Total Bilirubin (mg/dL)		≥ 2.0
Total Protein (g/dL)	≤ 4.5	≥ 10
Triglycerides (mg/dL)		≥ 600
Uric acid (mg/dL)		
Female		≥ 8.5
Male		≥ 10.5

ULN = Upper limit of normal

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

75

Appendix I (Cont.)

Urinalysis	Very Low	Very High
Specific Gravity	≤ 1.001	≥ 1.030
PH	≤ 4	≥ 9
Protein		$\geq 3+^*$ (≥ 10)
Ketones		$\geq 3+^*$
RBC		
Female		$\geq 10/\text{hpf}$
Male		$\geq 8/\text{hpf}$
WBC		$\geq 10/\text{hpf}$ ($\geq 2+$)
Casts		≥ 9
Glucose		$\geq 3+^*$
Oral Body Temperature		
Temperature	Low: decreased $\geq 2^\circ\text{F}$ from baseline High: $\geq 101^\circ\text{F}$ and increased $\geq 2^\circ\text{F}$ from baseline	
Body Weight		
Weight	Low: decreased $\geq 15\%$ from baseline High: increased $\geq 15\%$ from baseline	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mmHg and decreased ≥ 30 from baseline High: ≥ 180 mmHg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mmHg and decreased ≥ 20 from baseline High: ≥ 105 mmHg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	
Orthostatic Vital Signs		
Systolic Blood Pressure	Low: ≤ 86 mmHg and decreased ≥ 30 from supine	
Heart rate	High: ≥ 130 bpm and increased ≥ 20 bpm from supine	

* $\geq 3+$ on a scale with 4+ being the maximum value

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-826
 Incorporating Amendment Numbers One and Two - 12/22/98

76

Appendix I (Cont.)

Electrocardiogram	
PR Interval	High: ≥ 210 msec
QRS Duration	Low: ≤ 50 msec
	High: ≥ 150 msec
QT Interval	Low: ≤ 200 msec
	High: ≥ 500 msec
QTc Interval*	Low: ≤ 200 msec
	High: ≥ 500 msec
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline

* QTc calculated as QT divided by the square root of RR interval

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

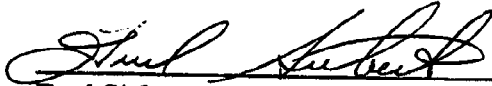
Part 1

ABBOTT LABORATORIES
Clinical Protocol

**A Randomized, Double Blind, Placebo-Controlled, Comparison
of the Safety and Efficacy of ABT-594 to Placebo in Patients
with Painful Polyneuropathies**

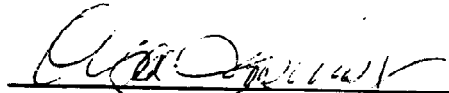
Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999




Fred Siebert, MT-BB (ASCP)
Senior Clinical Research Associate, Analgesia Venture

1-6-99
Date



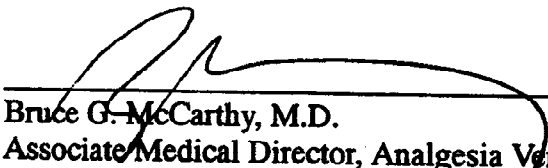
Olga Jasinsky
Senior Operations Manager, Analgesia Venture

1-5-99
Date



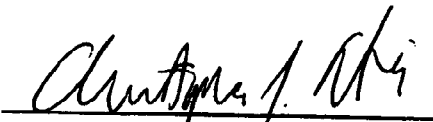
David Morris, Ph.D.
Manager, Clinical Statistics

1-7-99
Date



Bruce G. McCarthy, M.D.
Associate Medical Director, Analgesia Venture

1/6/99
Date



Christopher J. Silber, M.D.
Venture Head, Analgesia Venture

1/6/99
Date

 **Abbott Laboratories**

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABBOTT LABORATORIES
CLINICAL PROTOCOL
INVESTIGATIONAL NEW DRUG
ABT-594

PROTOCOL M98-833

**A Randomized, Double Blind, Placebo-Controlled, Comparison
of the Safety and Efficacy of ABT-594 to Placebo in Patients
with Painful Polyneuropathies**

Amendment No. Two - January 5, 1999

The purpose of this amendment is to:

- Delete inclusion criteria that specifies patients must be non-smokers and non-nicotine users.
- Remove reference to nicotine use throughout the protocol.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Amendment No. Two - January 5, 1999

2

Specific Protocol Changes:

**Section 2.0 Study Synopsis, Diagnosis and Main Criteria for Inclusion,
Fourth Bullet Point**

Delete:

- The patient must be a non-smoker or not have smoked or used nicotine by other means (i.e., chewing tobacco, nicotine gum or patch) within two months before dosing.

Section 9.3.1 Inclusion Criteria, Subsections 9.3.1.5

Delete:

- 9.3.1.5 The patient must be a non-smoker or not have smoked or used nicotine by other means (i.e., chewing tobacco, nicotine gum or patch) within two months before dosing.

Re-number subsections that follow 9.3.1.5.

Section 9.4.7 Prior and Concomitant Therapy, Second Paragraph

Delete:

Patients, who have used nicotine-containing products within two months of randomization, will not be eligible for inclusion in this study. Patients will not be allowed to use nicotine-containing products during this study.

Section 9.5.1.2 Safety Measurements and Procedures, Medical History, Last Sentence
Change:

The medical history (including medication and nicotine use) will be updated at the Baseline Visit (Day 1).

To read:

The medical history will be updated at the Baseline Visit (Day 1).

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

1.0 Title Page

Abbott Laboratories
Analgesia Venture, D48Q
Clinical Study

A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Patients with Painful Polyneuropathies

ABT-594/M98-833
Incorporating Amendment No. One - November 23, 1998

Development Phase: II

Investigators: Multicenter Trial

Date First Patient Dosed: October 1998

Date Last Patient Completed Dosing: February 1999

Sponsor/Emergency Contact: Christopher J. Silber, M.D.
Venture Head,
Analgesia Venture
Phone: (847) 938-5236, Fax: (847) 938-5258
Analgesia Venture, Department 48Q
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

This study will be conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

Confidential Information

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

ii

2.0 Study Synopsis

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Part of the Dossier: Not Applicable (N/A) Volume: N/A Page: N/A	(For National Authority Use Only)
Title of Study: A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Patients with Painful Polyneuropathies		
Investigator(s): Multicenter Study		
Study Center(s): Multicenter Study		
Publication (reference): N/A		
Study Period (years): Estimated Date of First Enrollment: 10/98 Estimated Date of Last Enrollment: 02/99		Phase of Development: II
Objectives: The objective of this study is to compare the safety and analgesic efficacy of 25 µg and 75 µg twice daily (BID) of ABT-594 to placebo in patients who have painful polyneuropathy, have moderate or severe pain (by the four point Daily Pain Intensity Categorical Scale) everyday during the Baseline Pain Assessment Period, have moderate or severe pain (by the four point Pain Intensity Categorical Scale) at the Baseline Visit, and who are not taking another analgesic concurrently.		
Methodology: This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in patients with painful polyneuropathy. Approximately 150 patients will be assigned randomly in an equal ratio to receive either ABT-594 BID (25 µg or 75 µg), or placebo for 22 days on an outpatient basis. Approximately 10 sites will be recruited in order to enroll 150 patients who meet entry criteria for this study. Prior to study drug administration, patients will have discontinued all analgesic medications and have completed a 4 day Washout Period and a 3 day Baseline Pain Assessment Period. Patients will then receive study medication for 22 days (Treatment Phase), during which time they will return to the site weekly (Treatment Visits I, II and III). Patients will complete diary-based assessments of their neuropathy pain each day from the three days prior to study drug administration (Baseline Pain Assessment Period) through Day 21 of study drug administration. In addition, patients will undergo site-based assessments of their neuropathy pain at the Baseline Visit and Treatment Visits I, II and III. Patients will discontinue study drug administration after Treatment Visit III and return to the site for the Follow-Up visit 7-10 days later. See Figure 9.1a, Study Schematic, for additional study layout information.		

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

iii

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Part of the Dossier: Not Applicable (N/A) Volume: N/A Page: N/A	(For National Authority Use Only)
Methodology: (Continued) Diary-based assessments will include the Daily Pain Intensity Categorical Scale and VAS. Site-based assessments will include the Pain Intensity Categorical Scale and VAS, the Neuropathic Pain Scale, and the Patient Global Evaluation (the latter only at Treatment Visit III).		
No. of Patients: 150		
Diagnosis and Main Criteria for Inclusion: A patient may be randomized in this study provided that he/she meets all of the Inclusion Criteria outlined below and does not meet any of the Exclusion Criteria in Section 9.3.2. <ul style="list-style-type: none"> • The patient must be between the ages of 18 and 75 years of age, inclusive. • The patient's weight must be between 100 lbs and 265 lbs, inclusive, with weight proportional to height as judged by the investigator. • A female patient must be non-lactating and: <ul style="list-style-type: none"> - of non-childbearing potential (either postmenopausal for at least one year or surgically sterile, including tubal ligation), <li style="text-align: center;">OR - of childbearing potential using oral or barrier contraceptive methods for at least two months preceding randomization (and must continue contraceptive method through the course of the study). <p>All female patients must have a negative β subunit human chorionic gonadotropin (β-hCG) at the screening, baseline and treatment visits.</p> <ul style="list-style-type: none"> • The patient must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy. • The patient's pain quality and location are consistent with the polyneuropathy (in 9.3.1.5), in the opinion of the investigator. • The patient's neuropathy symptoms (including pain) have been stable for at least the last three months prior to the Screening Visit (defined by the opinion of the investigator). • The patient must have moderate or severe pain (by the four-point Daily Pain Intensity Categorical Scale) everyday during the Baseline Pain Assessment Period and moderate or severe pain (by the four-point Pain Intensity Categorical Scale) at the Baseline Visit. 		

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

iv

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Part of the Dossier: Not Applicable (N/A) Volume: N/A Page: N/A	(For National Authority Use Only)						
Test Product(s): ABT-594 25 µg and 50 µg SEC. Dose: ABT-594 25 µg or 75 µg BID (Section 9.4.1) Mode of Administration: Oral								
Batch Number: <table border="1" data-bbox="518 751 1166 890"> <thead> <tr> <th>Study Drug</th> <th>Drug Product Lot Number</th> </tr> </thead> <tbody> <tr> <td>ABT-594 25 µg SEC</td> <td>39-904-AR-R1</td> </tr> <tr> <td>ABT-594 50 µg SEC</td> <td>39-905-AR-R1</td> </tr> </tbody> </table>			Study Drug	Drug Product Lot Number	ABT-594 25 µg SEC	39-904-AR-R1	ABT-594 50 µg SEC	39-905-AR-R1
Study Drug	Drug Product Lot Number							
ABT-594 25 µg SEC	39-904-AR-R1							
ABT-594 50 µg SEC	39-905-AR-R1							
Duration of Treatment: 22 days								
Reference Therapy: Placebo for ABT-594 SEC Dose: Placebo to match test product (see Section 9.4.1) Mode of Administration: Oral Batch Number: <table border="1" data-bbox="514 1155 1208 1251"> <thead> <tr> <th>Study Drug</th> <th>Drug Product Lot Number</th> </tr> </thead> <tbody> <tr> <td>Placebo for ABT-594 SEC</td> <td>39-903-AR-R1</td> </tr> </tbody> </table>			Study Drug	Drug Product Lot Number	Placebo for ABT-594 SEC	39-903-AR-R1		
Study Drug	Drug Product Lot Number							
Placebo for ABT-594 SEC	39-903-AR-R1							

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

v

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Soft Elastic Capsule (SEC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Part of the Dossier: Not Applicable (N/A) Volume: N/A Page: N/A	(For National Authority Use Only)
Criteria for Evaluations: Efficacy: Daily Pain Intensity (four-point categorical scale and VAS, both diary-based), Pain Intensity (four-point categorical scale and VAS, both site-based), Neuropathic Pain Scale, and Patient Global Evaluation. Safety: Medical history, physical exam, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.		
Statistical Methods: For all safety and efficacy analyses, the primary comparison will be between ABT-594 and placebo. Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the treatment groups using analysis of variance (ANOVA) and Fisher's exact test, as appropriate. Treatment emergent adverse events will be summarized by body system and COSTART term and compared using Fisher's exact test. The primary and secondary efficacy variables, including change from baseline pain scores and change from baseline to the total of the Neuropathic Pain Scale, will be analyzed by using appropriate parametric and nonparametric methods. The final global evaluation score will be compared using Cochran-Mantel-Haenszel methodology. Other efficacy analyses will be performed as appropriate. Laboratory data that are low or high will be flagged in the data listings. In addition, all potentially clinically significant laboratory, ECG and vital sign data will be identified.		

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

vi

3.0 Table of Contents

	Page
1.0 Title Page	i
2.0 Study Synopsis	ii
3.0 Table of Contents	vi
4.0 List of Abbreviations and Definitions of Terms	x
5.0 Ethics	1
5.1 Institutional Review Board or Independent Ethics Committee ..	1
5.2 Ethical Conduct of the Study	1
5.3 Patient Information and Consent	1
5.4 Patient Confidentiality	2
6.0 Investigators and Study Administrative Structure	3
6.1 Investigative Sites	3
6.2 Sponsor Information	3
6.3 Clinical Supply Management	3
6.4 Central Laboratory	4
6.5 Administrative Structure	4
7.0 Introduction	6
7.1 Analgesia Today	6
7.2 ABT-594	6
8.0 Study Objectives	10
9.0 Investigational Plan	10
9.1 Overall Study Design and Plan: Description	10
9.2 Discussion of Study Design	14
9.3 Selection of Study Population	14
9.3.1 Inclusion Criteria	14
9.3.2 Exclusion Criteria	15

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

vii

Table of Contents (Continued)

	Page
9.3.3 Removal of Patients from Therapy	17
9.4 Treatments	17
9.4.1 Treatments Administered	17
9.4.2 Identity of Investigational Products	18
9.4.2.1 Packaging and Labeling	19
9.4.2.2 Storage and Disposition of Supplies	19
9.4.2.3 Drug Accountability	19
9.4.3 Method of Assigning Patients to Treatment Groups	20
9.4.4 Selection of Doses in the Study	20
9.4.5 Selection and Timing of Dose for Each Patient	20
9.4.6 Blinding	21
9.4.7 Prior and Concomitant Therapy	21
9.4.8 Treatment Compliance	22
9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures	22
9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts	22
9.5.1.1 Efficacy Measurements	24
9.5.1.2 Safety Measurements and Procedures	25
9.5.1.2.1 Adverse Events	29
9.5.1.2.2 Serious Adverse Events	31
9.5.2 Appropriateness of Measurements	33
9.5.3 Efficacy Variables	33
9.5.3.1 Primary Variable(s)	34
9.5.3.2 Secondary Variable(s)	34
9.5.4 Blood Samples for Genetic Polymorphism Analysis	34

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

viii

Table of Contents (Continued)

	Page
9.6 Data Quality Assurance	35
9.7 Statistical Methods and Determination of Sample Size	36
9.7.1 Statistical and Analytical Plans	36
9.7.1.1 Data Sets Analyzed	36
9.7.1.2 Demographic and Other Baseline Characteristics	37
9.7.1.3 Efficacy Analyses	37
9.7.1.4 Safety	38
9.7.2 Determination of Sample Size	39
9.8 Changes in the Conduct of the Study or Planned Analyses	39
9.8.1 Protocol Changes	39
10.0 Protocol Deviations	40
11.0 Use of Information and Publication	40
12.0 Completion of The Study	41
13.0 Investigator's Agreement	42
14.0 References	43

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two – January 5, 1999

ix

Table of Contents (Continued)

	Page
List of Tables	
Table 9.4.1a	Number and Type of Capsules by Treatment Regimen
	18
Table 9.4.2a	Identity of Investigational Products
	18
Table 9.5a	Study Procedures Flow Chart
	23
Table 9.5b	Clinical Laboratory Tests
	27
Table 9.5c	Definitions for Investigator Rating of Adverse Event Severity
	30
Table 9.5d	Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug
	30

List of Figures

Figure 6.5a	Administrative Structure	5
Figure 9.1a	Study Schematic	13

List of Appendices

Appendix A	Documents Required Prior to Initiation of the Study	44
Appendix B	Declaration of Helsinki	45
Appendix C	Responsibilities of the Clinical Investigator	49
Appendix D	Elements of the Consent Form	50
Appendix E	Sample Abbott Laboratories Drug Accountability Form ..	53
Appendix F	Pain Assessments	54
Appendix G	Neuropathic Pain Scale	57
Appendix H	Potentially Clinically Significant Values for Laboratory Determinations, Vital Signs and Electrocardiogram Variables	59

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

x

4.0 List of Abbreviations and Definitions of Terms

List of Abbreviations

ABT-594	[(R)-5-(2-azetidylmethoxy)-2-chloropyridine] or A-165594
ANOVA	Analysis of Variance
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transminase
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transminase
BID	<i>bis in die</i> , twice a day
bpm	Beats per minute
BUN	Blood urea nitrogen
°C	Degrees Centigrade
cc	Cubic centimeter
Cont.	Continued
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CSI	Clinical Supplies Invoice
D	Day
dL	Deciliter
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EEC	European Economic Community
FDA	Food and Drug Administration
°F	Degrees Fahrenheit
fL	Femtoliter
g	Gram
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
hpf	High Powered Field
hrs	Hours
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International units
kg	kilogram

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

xi

List of Abbreviations and Definitions of Terms (Continued)

L	Liter
lbs	Pounds
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
µg/mcg	Microgram
mEq	Milliequivalents
mg	Milligrams
min	Minutes
mL	Milliliter
mm	Millimeter
mm Hg	Millimeters of mercury
msec	Millisecond
N/A	Not applicable
nAChRs	Neuronal nicotinic acetylcholine receptors
NPRO	New Product Research Order
NPS	Neuropathic Pain Scale
NSAID	Nonsteroidal anti-inflammatory drug
OC	Observed cases
OTC	Over-the-counter
PPD	Pharmaceutical Products Division
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SEC	Soft Elastic Capsule
sec	Second
SOP	Standard Operating Procedure
SSRI	Serotonin-specific reuptake inhibitor
STD	Standard Deviation
TCA	Tricyclic antidepressant
TENS	Transcutaneous Electrical Nerve Stimulation

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

xii

List of Abbreviations and Definitions of Terms
(Continued)

ULN	Upper limit of normal
VA	Visual Analog
VAS	Visual Analog Scale
WBC	White blood cell

Terms

AUC	Area under the plasma concentration-time curve
C _{max}	Maximum observed concentration
NOMAD [®]	A validated data management system

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

1

5.0 Ethics

5.1 Institutional Review Board or Independent Ethics Committee

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human patients in research. The investigator will obtain a duly constituted IRB review and approval of the protocol, informed consent form and all other forms of patient information related to the study (e.g., advertisements used to recruit patients). Abbott Laboratories will receive documentation of the study approval, the signed signature page from the study protocol, patient informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year. A complete list of documents required prior to initiation of the study is located in Appendix A.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version, Appendix B) and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix C.

5.3 Patient Information and Consent

The investigator or his/her representative will explain the nature of the study to the patient, and answer all questions regarding this study. Prior to any screening procedures being performed on the patient, the informed consent statement will be reviewed and signed and dated by the patient and the person who administered the informed consent.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

2

A copy of the informed consent form will be given to the patient and a copy will be placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the patient received a signed copy. Elements of an Informed Consent are specified in Appendix D.

5.4 Patient Confidentiality

All reports and communications relating to patients in the study will identify each patient only by the patient's initials (first, middle, last) and by the patient's study number. Case report forms (CRF) will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the patient's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the CRFs.

The site will collect information on the patient per International Council on Harmonization (ICH) requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency should also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site according to the record retention guidelines outlined in Section 12.0.

Neither the patient, the patient's physician, nor the investigator will be informed of the patient's pharmacogenetic results, should they be obtained. If performed, results from individual patients will be kept confidential and will not be given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples will be stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples will be kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

3

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Investigative sites will be selected by Abbott Laboratories. Approximately 10 sites will be selected to enroll patients for this study. Investigators will be selected on their ability to enroll patients as well as the adequacy of their sites to manage study related activities and requirements.

6.2 Sponsor Information

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this multicenter clinical study. The protocol, CRFs and sample informed consent form will be generated by Abbott Laboratories. Abbott will coordinate and perform all site visits and will prepare trip reports for each visit performed. These reports will detail the activities conducted at all investigative sites and will include all relevant observations. The database for this study will be created using NOMAD[®], a validated data management system. Designated statisticians from Abbott Laboratories will be responsible for the statistical analysis of the data.

6.3 Clinical Supply Management

Clinical supplies will be prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories will authorize the release of clinical supplies once the appropriate essential documents have been received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs. The site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records (Appendix E), and records for return of used and unused clinical supplies to Abbott Laboratories. Monitors will check drug accountability records regularly.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

4

6.4 Central Laboratory

This study will utilize one central laboratory. All protocol specified clinical laboratory tests will be performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

6.5 Administrative Structure

The administrative structure for this study is depicted in Figure 6.5a.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

5

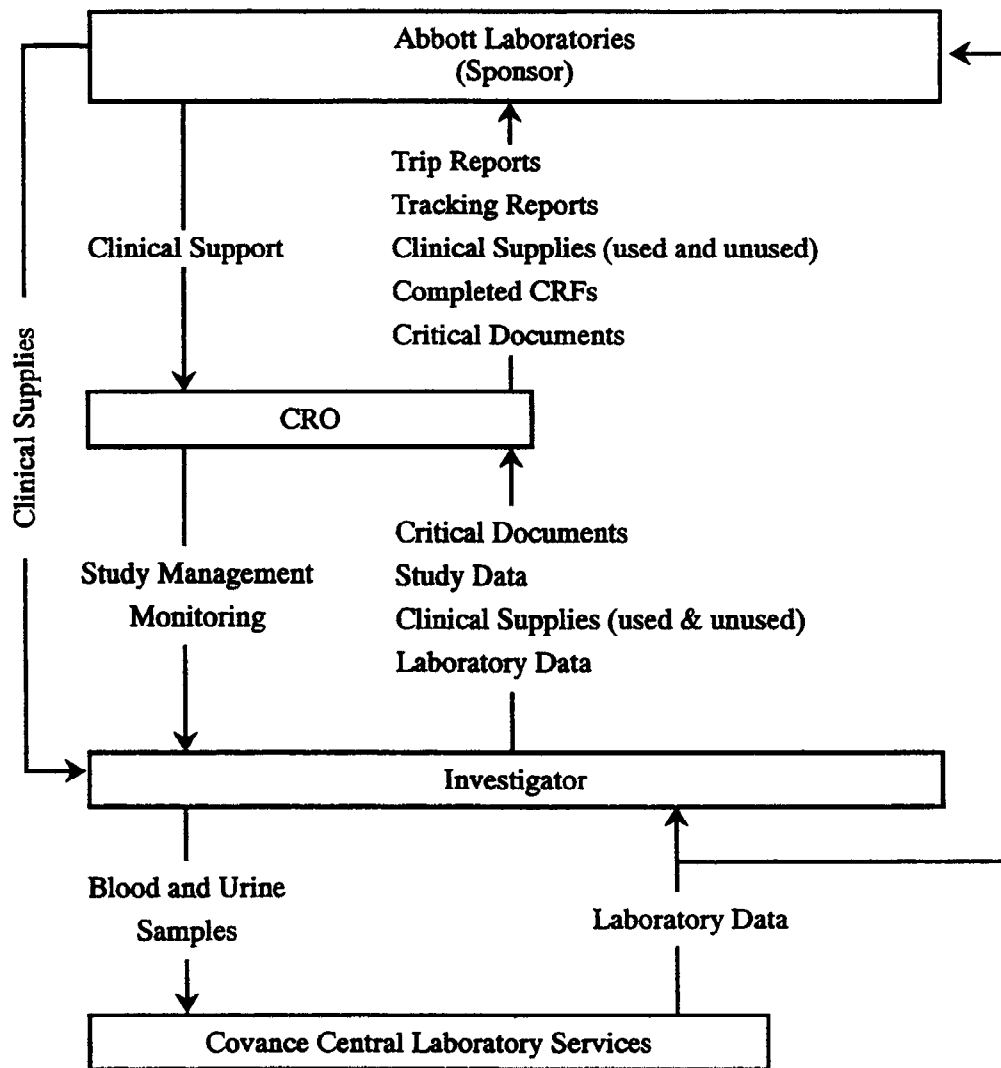


Figure 6.5a Administrative Structure

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

6

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. In the United States, millions of operations are performed annually, most involving some form of acute pain management. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹ For patients with cancer, it has been estimated that pain is experienced by 20% to 50% of patients at the time of their diagnosis, with up to 75% of those with advanced cancer experiencing pain.²

Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in patients receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (\pm)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

7

morphine in rodent models of antinociception.³ The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.⁴ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

8

To date, four completed Phase I studies have evaluated the safety, tolerability, and pharmacokinetics of ABT-594 single dose (Study M97-676) and multiple dose (Study M97-743) administration, the effect of food on the bioavailability of single doses of ABT-594 oral solution (Study M97-787) and soft elastic capsule (SEC) formulations (Study M97-706), and the comparative bioavailability of these initial oral liquid and solid soft elastic capsule (SEC) formulations (Study M97-706). In these studies, approximately 151 subjects have received at least one dose of ABT-594 (25 µg to 200 µg) under fasted (i.e., after a 10-hour fast) or fed conditions (i.e., approximately 30 minutes after a meal was served).

In Study M97-676, a double-blind, placebo-controlled, single rising dose study, 53 subjects in eight dosing groups received a single fixed dose of an oral solution of ABT-594 (30 µg to 200 µg) under fasted or fed conditions. Twenty-four placebo subjects were also involved in the study. In each dose group, up to seven subjects received ABT-594 and three subjects received placebo. Thirty-five normal healthy males received either 30 µg, 50 µg, 80 µg, 100 µg, or 150 µg of ABT-594 under fasted conditions. Thirteen normal healthy males received either 150 µg or 200 µg of ABT-594 under fed conditions. Five surgically-sterilized females received 80 µg of ABT-594 under fed conditions.

Dosing in males could not proceed beyond the 150 µg level under fasted conditions due to emesis, but the 150 µg dose administered under fed conditions was well tolerated. Approximately 60% of ABT-594 subjects and 50% of placebo subjects experienced at least one adverse event. The most frequently noted adverse events were dizziness, nausea, headache, vomiting, pallor, somnolence, sweating, diarrhea, paresthesia, vasodilation, and vertigo. Events of headache, vasodilation, diarrhea, and vertigo were evident at comparable levels in placebo subjects. Pharmacokinetic analysis suggests that ABT-594 shows relatively linear pharmacokinetics at doses up to 150 µg under fasted conditions and that approximately 50% of ABT-594 is excreted in the urine. No effect of gender or feeding condition was evident on pharmacokinetic parameters. ABT-594 was generally well-tolerated at doses up to 100 µg in subjects who were fasted and at 150 µg in subjects who were fed prior to dosing.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

9

In Study M97-743, a double-blind, placebo-controlled multiple rising dose study, 54 normal healthy male subjects in seven dosing groups received a single fixed daily dose of an oral solution of ABT-594 (25 µg to 150 µg) for up to 14 consecutive days under fasted or fed conditions. An additional eight subjects in a twice daily dosing group (Group 8) received two single fixed daily doses, twelve hours apart, of ABT-594 75 µg for up to 14 consecutive days under fed conditions. Thirty-two placebo subjects were also involved in the study. Within each dose group, up to eight subjects received ABT-594 and four subjects received placebo.

Four ABT-594 subjects were prematurely terminated from the M97-743 study. One subject who received a single dose of 75 µg of ABT-594 had a presyncopal episode with pallor, bradycardia, hypotension, and telemetry findings of a 15-second third degree heartblock upon orthostasis, thought to be of possible vasovagal etiology. One subject in the 100 µg fasted dose group was discontinued on Day 8 due to fever and anxiety. In the 100 µg fed dose group, one subject was discontinued on Day 8 due to transaminase elevation greater than three times the upper limit of normal. One subject who received 75 µg of ABT-594 twice daily was discontinued on Day 5 due to sinus tachycardia upon orthostasis.

Initial emesis occurred in four subjects at the 100 µg dose level under fasted conditions, but increased tolerability was noted with repeat dosing and in the 100 µg, 125 µg, and 150 µg dose groups under fed conditions. Approximately 90% of placebo subjects and 89% of ABT-594 subjects had at least one report of an adverse event during the 14-day dosing period. Upon preliminary review, the most frequent events reported for ABT-594 subjects were headache, nausea, dizziness, brief postdosing oral sensation, somnolence, asthenia, vomiting, vasodilation, taste perversion, rhinitis, abnormal thinking, flatulence, paresthesia, sweating, and infection. Other events reported by at least three ABT-594 subjects were injection site pain, orthostatic hypotension, dry mouth, dyspepsia, insomnia, pharyngitis, chest pain, pallor, anorexia, diarrhea, eructation, myalgia, ataxia, epistaxis, abdominal pain, fever, pain, palpitations, hypertonia, incoordination, dyspnea, and dry skin. Events such as headache, somnolence, rhinitis, infection, pharyngitis, insomnia, diarrhea, and abdominal pain were also present at a comparable or greater level in placebo subjects.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

10

In Study M97-787, an open-label, two-period crossover study, the effect of food on the bioavailability of an oral solution of ABT-594 after administration of a single 80 µg dose was evaluated in 12 normal healthy male subjects. In Study M97-706, an open-label, four-period study, the comparative bioavailability of three formulations of ABT-594 (liquid, 25 µg and 50 µg SECs) and the effect of food on the SEC bioavailability after administration of single 100 µg doses were evaluated in 24 normal healthy males. In both studies, the preliminary safety and tolerability profile showed no differences from previous studies. In addition, preliminary data suggest bioequivalence between the formulations and no effect of feeding condition on the pharmacokinetic profile of the 50 µg SEC.

Initial Phase I studies have provided preliminary data in support of the safety and tolerability of ABT-594. A Phase II study (M97-772), that will evaluate the analgesic efficacy of ABT-594 in pain after molar extraction, is currently ongoing. This study (M98-833) is one of several additional Phase II studies that will characterize more fully the analgesic efficacy of ABT-594.

8.0 Study Objectives

The objective of this study is to compare the safety and analgesic efficacy of 25 µg and 75 µg twice daily (BID) of ABT-594 to placebo in patients who have painful polyneuropathy, have moderate or severe pain (by the four point Daily Pain Intensity Categorical Scale) everyday during the Baseline Pain Assessment Period, have moderate or severe pain (by the four point Pain Intensity Categorical Scale) at the Baseline Visit, and who are not taking another analgesic concurrently.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This is a phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in patients who have painful polyneuropathy. Approximately 150 patients will be assigned randomly in an equal ratio

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

11

to receive one of three treatments: ABT-594 25 µg, 75 µg or placebo BID for 22 days on an outpatient basis. Approximately 10 sites will be recruited in order to enroll approximately 150 patients who meet entry criteria for this study.

The study will be divided into four phases: Screening Phase (Day -22 to Day -8), Pre-Treatment Phase (Day -7 to Day -1), Treatment Phase (Day 1 to Day 22) and Post-Treatment Phase (Day 23 to Day 32). The Pre-Treatment Phase is further subdivided into the Washout Period (Day -7 to Day -4) and the Baseline Pain Assessment Period (Day -3 to Day -1). Day 1 is the first day of study drug administration. Patients will be allowed a window of ± 1 day for each study visit. The study design is depicted in Figure 9.1a.

Patients will review and sign the informed consent prior to the conduct of any study specific procedures. Patients will then be screened for eligibility by medical history, physical examination, vital sign measurements, electrocardiogram (ECG), and clinical laboratory tests. Those patients taking tricyclics, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs (AEDs), or other analgesics for the treatment of their pain, will begin titration off of these medications and will not enter the Washout Period until these medications have been discontinued. After discontinuing all analgesics, patients will enter the Pre-Treatment Phase, which will last seven days and consists of a Washout Period and a Baseline Pain Assessment Period. The Washout Period will last four days and will start on Day -7. During the Baseline Pain Assessment Period (Day -3 to Day -1), patients will complete, at approximately 9 P.M. each evening, diary-based assessments of neuropathic pain intensity: the Daily Pain Intensity Categorical Scale and the Daily Pain Intensity Visual Analog Scale (VAS, Appendix F).

On the day after the Baseline Pain Assessment Period, patients will return to the site for their Baseline Visit (Day 1). During this visit, patients will undergo an interim medical history, physical examination, vital sign measurements, ECG and clinical laboratory tests. Study site personnel will collect patients' study diaries. Patients will complete site based-assessments prior to study drug administration: Pain Intensity Categorical Scale and VAS and the Neuropathic Pain Scale (NPS, Appendix G). Patients who meet all entry criteria, including moderate or severe pain (by the four-point Daily Pain Intensity

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

12

Categorical Scale) every day during the Baseline Pain Assessment Period and moderate or severe pain (by the four-point Pain Intensity Categorical Scale) at the Baseline Visit, will be randomized into one of the following treatment groups: ABT-594 25 µg BID, ABT-594 75 µg BID or placebo BID. Patients will also receive their next set of diaries.

Patients will start study drug at the next dosing time on Day 1 (as specified in Section 9.4.5) and continue for a total of 22 days. Patients will complete diary based assessments each evening (approximately 9 PM), two hours after taking their evening dose of study drug. They will return to the site for study procedures at the end of Week 1 (Day 8, Treatment Visit I), Week 2 (Day 15, Treatment Visit II) and Week 3 (Day 22, Treatment Visit III). Procedures during Treatment Visits I, II and III will include collection of diaries (and issuance of the next set at Treatment Visits I and II), site based assessments (including the Patient Global Evaluation at Treatment Visit III), physical examination (Treatment Visit III), vital sign measurements, ECG (Treatment Visit III), and clinical laboratory tests.

On the day after Treatment Visit III, patients will enter the Post-Treatment Phase. Patients will no longer take study drug or complete pain scales. Patients may restart all discontinued medication under the guidance of their physician. Patients will return for study procedures at the Follow-up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-up Visit will include physical examination, vital sign measurements, recording of any adverse events since Treatment Visit III and reexamination of any abnormal findings (by ECG or clinical laboratory tests) present at the previous evaluation.

For those patients who participate in clinical studies of ABT-594 and who consent, a blood sample will be collected in order to obtain a sample of genetic material (DNA). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way patients respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful distal symmetric polyneuropathies.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

13

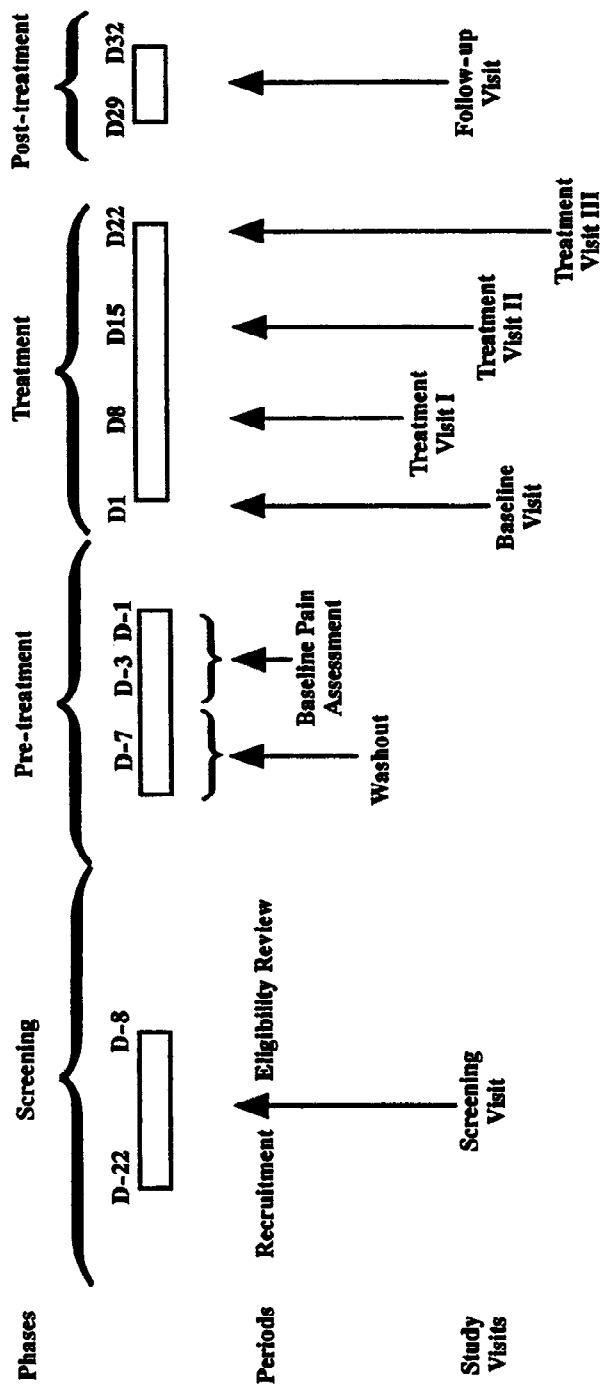


Figure 9.1a Study Schematic

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

14

9.2 Discussion of Study Design

The design of this study provides a placebo control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales will be employed.

The study design includes several similar but distinct efficacy measures in two different settings: diary-based and site-based assessments. Diary-based assessments include the four-point Daily Pain Intensity Categorical Scale and the Daily Pain Intensity VAS. Site-based assessments include the four-point Pain Intensity Categorical Scale, the Pain Intensity VAS, the NPS and the Patient Global Evaluation (the latter only at Treatment Visit III).

A washout period is included because the patients sought for inclusion in this study are likely to be taking analgesic medications prior to study start. Patients are unlikely, however, to tolerate moderate or severe pain for extended periods necessary to achieve a complete washout and the four day Washout Period represents a compromise.

9.3 Selection of Study Population

It is anticipated that approximately 150 patients will be randomized and receive study medication in this study. A patient may be randomized in this study provided that he/she meets all of the inclusion criteria outlined in Section 9.3.1 and does not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

- 9.3.1.1 Prior to any study specific procedure, voluntary written informed consent must be obtained from the patient after the purpose and nature of the study have been explained.
- 9.3.1.2 The patient must be between the ages of 18 and 75 years of age, inclusive.
- 9.3.1.3 The patient's weight must be between 100 lbs and 265 lbs, inclusive, with weight proportional to height as judged by the investigator.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

15

9.3.1.4 A female patient must be non-lactating and:

- of non-childbearing potential (either postmenopausal for at least one year or surgically sterile, including tubal ligation),

OR

- of childbearing potential using oral or barrier contraceptive methods for at least two months preceding randomization (and must continue contraceptive method through the course of the study).

All female patients must have a negative β subunit human chorionic gonadotropin (β -hCG) at the screening, baseline and treatment visits.

9.3.1.5 The patient must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.**9.3.1.6 The patient's pain quality and location are consistent with the polyneuropathy (in 9.3.1.5), in the opinion of the investigator.****9.3.1.7 The patient's neuropathy symptoms (including pain) have been stable for at least the last three months prior to the Screening Visit (defined by the opinion of the investigator).****9.3.1.8 The patient must have moderate or severe pain (by the four-point Daily Pain Intensity Categorical Scale) every day during the Baseline Pain Assessment Period and moderate or severe pain (by the four-point Pain Intensity Categorical Scale) at the Baseline Visit.****9.3.2 Exclusion Criteria****9.3.2.1 The patient has positive test results for drugs of abuse or viral hepatitis at the Screening Visit or has a known history of a positive test result for HIV****9.3.2.2 The patient has a history of drug or alcohol abuse or dependence.****9.3.2.3 The patient consumes more than two alcoholic drinks each day (where an alcoholic drink is 4 ounces of wine, 10 ounces of 5.7% beer or a 1.25 ounce shot of 80 proof liquor) by patient history.**

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

16

- 9.3.2.4 The patient has a history of epilepsy, any clinically significant cardiac, respiratory (except mild asthma), renal, hepatic, gastrointestinal, hematologic, or psychiatric disease or disorder, or any uncontrolled medical illness.
- 9.3.2.5 The patient has received an investigational drug within three months prior to administration of study treatment or is scheduled to receive an investigational drug other than ABT-594 during the course of this study.
- 9.3.2.6 The patient has a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.
- 9.3.2.7 The patient has orthostatic hypotension at the Screening Visit (as defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after one minute of standing), or a history of syncope or pre-syncope symptoms.
- 9.3.2.8 The patient has participated previously in a study involving ABT-594, including the present study.
- 9.3.2.9 The patient has a clinically significant abnormality in clinical chemistry, hematology, or urinalysis, including AST or ALT ≥ 1.5 the upper limit of the reference range or calculated creatinine clearance ≤ 60 mL/minute. Patients with diabetes mellitus may have elevated serum and urine glucose, but their serum glucose must have been under good control (in the opinion of the investigator) for at least the last three months prior to the Screening visit.
- 9.3.2.10 The patient has clinically significant electrocardiographic abnormalities.
- 9.3.2.11 Ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7.
- 9.3.2.12 Diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study).

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

17

9.3.2.13 Patients with sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.

9.3.2.14 Patients who, in the opinion of the investigator, are unlikely to comply with the study protocol or who are unsuitable for any other reason.

9.3.3 Removal of Patients from Therapy

A patient may voluntarily terminate participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to terminate prematurely a patient's participation. The investigator must notify the clinical research associate (CRA) within 24 hours and document the reason for premature termination on the appropriate CRF.

Patients, whose participation is terminated prematurely after signing study consent but before study drug administration, will not require follow-up observations. Patients, whose participation is terminated prematurely after study drug administration and prior to Treatment Visit III, must undergo procedures normally performed at Treatment Visit III (see Table 9.5a) within 7-10 days of termination from the study.

If, in the judgment of the investigator or Abbott Laboratories, continued exposure to a study drug represents a significant risk to patients, the study will be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Patients will be randomly assigned in an equal ratio to one of the following three treatment groups:

ABT-594 25 µg BID

ABT-594 75 µg BID

Placebo

ABT-594 and matching placebo will be supplied as soft elastic capsules (SEC).

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

18

Patients will receive two SEC (one capsule from Bottle A and one capsule from Bottle B) BID for 22 days.

Table 9.4.1a Number and Type of Capsules by Treatment Regimen

Treatment Regimen	Number of Capsules Per Dose					
	Bottle A ¹ (BID)			Bottle B ¹ (BID)		
	25 µg ABT-594 SEC	50 µg ABT-594 SEC	Placebo ABT-594 SEC	25 µg ABT-594 SEC	50 µg ABT-594 SEC	Placebo ABT-594 SEC
ABT-594 25 µg	1	0	0	0	0	1
ABT-594 75 µg	1	0	0	0	1	0
Placebo	0	0	1	0	0	1

¹ Store at 36-46°F. Refrigerate.

9.4.2 Identity of Investigational Products

Table 9.4.2a Identity of Investigational Products

Test Preparation Drug Product	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 25 µg SEC	39-904-AR-R1	27-335-YS-00	R.P. Scherer ¹
ABT-594 50 µg SEC	39-905-AR-R1	27-335-YS-00	R.P. Scherer ¹
ABT-594 placebo SEC	39-903-AR-R1	N/A	R.P. Scherer ¹

¹ St. Petersburg, FL

ABT-594 25 µg SEC, 50 µg SEC and placebo SEC are identical in appearance.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

19

9.4.2.1 Packaging and Labeling

All study drug supplies will be blinded and packaged in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). ABT-594 SEC and matching placebo will be packaged in bottles containing 20 capsules each. Two bottles, each containing 20 soft elastic capsules, will be provided to each patient at the Baseline Visit and Treatment Visits I and II.

Each bottle will be labeled with a single-panel blinded label that has been pre-printed with the study number, patient number, Abbott address, New Product Research Order (NPRO) number, contents, directions for use and storage conditions. Space will be provided on the label to record the patient initials and date dispensed.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies must be stored in a secure location until dispensed to a patient or until returned to Abbott Laboratories. ABT-594 study supplies (bottles containing SEC) must be refrigerated (36-46°F). Patients will be instructed to take the drug as prescribed and return the bottle to refrigeration as soon as possible.

9.4.2.3 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. Study drug will be dispensed in numerical order to each patient, who meets the enrollment criteria, by the investigator according to the patient numbers provided to each site (Section 9.4.3). The investigator or designee will record the patient number, patient initials and date dispensed to the patient on the Drug Accountability Form (Appendix E). The amount of study drug remaining will be recorded at Treatment Visits I, II and III for each patient on the site Drug Accountability Form. An accurate running inventory of study drug will be kept and will include the NPRO number, CSI number(s), the number of capsules dispensed and the date study drug was dispensed for each patient. An overall accountability of the study drug will be performed and verified by the

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

20

CRA throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for and returned to Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with the instructions of the CRA, will also be included in the shipment. The investigator agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator.

9.4.3 Method of Assigning Patients to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by the Department of Clinical Statistics at Abbott Laboratories. Approximately 150 patients will be randomized in an equal ratio to receive either ABT-594 25 µg BID, ABT-594 75 µg BID, or placebo. After meeting entry criteria on Day 1, patients will be assigned randomization numbers in ascending numerical sequence per investigator site as they are enrolled in the study.

9.4.4 Selection of Doses in the Study

ABT-594 doses (25 µg, 75 µg) were selected on the basis of Phase I tolerability studies and represent doses below the maximally tolerated dose. No human data exist to indicate ABT-594 doses that are efficacious in the relief of pain.

9.4.5 Selection and Timing of Dose for Each Patient

Patients will be assigned randomly to treatment groups as described in Section 9.4.3. Patients will take BID doses of ABT-594 25, 75 µg or ABT-594 placebo within 30 minutes following breakfast and dinner (e.g., 7 AM and 7 PM). Study drugs should be taken with at least one cup of water (240 cc).

No human data exist to indicate ABT-594 dosing frequencies that are efficacious in the relief of pain. The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

21

9.4.6 Blinding

Both the investigator and the patient will remain blinded to the patient's treatment throughout the course of the study. A label, which contains drug assignment, will be provided to the investigator in a separate sealed envelope for each patient. The sealed envelope will be retained by the study coordinator as part of the CRF. The study blind envelope may be broken if, in the opinion of the investigator, it is in the patient's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) **MUST** be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. The sponsor must then be notified within 48 hours of the blind being broken. The date, time, and reason for blind breakage must be recorded on the appropriate CRF.

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications (used over the prior two weeks) will be taken.

If the administration of any concurrent medication is necessary during the course of this study, the medication name, dosage information, frequency, dates of administration, and indication for use must be reported on the CRF.

Concomitant analgesics (prescription or over-the-counter [OTC]), including serotonin-specific reuptake inhibitors, tricyclic antidepressants and antiepileptic medications, will not be allowed. Other concomitant treatments not allowed in the study are TENS and topical analgesics.

Aspirin, 81 mg daily maximum, for primary prevention of thromboembolic events is permitted. Patients taking higher doses may be switched to 81 mg daily prior to the Pre-Treatment Phase if the change in dose does not alter the efficacy of the aspirin treatment for the indication for which it was prescribed (in the opinion of the investigator in consultation with the prescribing physician, if any). Patients, who take aspirin during the study, must remain on a stable daily dose of aspirin throughout the Pre-treatment and Treatment Phases of the study.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 3

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

22

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, patients will be instructed to return all drug containers (even if empty) to the study coordinator at Treatment Visits I, II and III. Compliance with study drug will be documented by the study coordinator on the appropriate CRF.

9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures

9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Study procedures will be performed as summarized in Table 9.5a.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

23

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase			Pre-Treatment Phase		Treatment Phase				Post-Treatment Phase	
	Screening Visit	Between D-22 and D-8	Washout Period D-7 to D-4	Baseline Pain Assessment Period D-3 to D-1	D1 to D22	Baseline Visit D1	Treatment Visit			D23 to D32	Follow-up Visit D29 to D32
							D8 I	D15 II	D22 III ^a		
Informed Consent	X										
Medical History	X					X ^b					
Physical Exam	X					X			X		X
Vital Signs	X ^c					X	X	X	X		X
ECG	X					X			X		X ^d
Clinical Laboratory Tests ^e	X					X	X	X	X		X ^d
Viral Hepatitis Screen	X										
Urine Drug and Alcohol Screen	X										
Pregnancy Test	X					X	X	X	X		
Genetic Polymorphism Sample						X					
Diary Issued	X					X	X	X	X		
Diary Collected						X	X	X	X		
Diary-Based Efficacy Measurements ^f					X ^{g,h}						
Site-Based Efficacy Measurements ^f						X	X	X	X		
Patient Global Evaluation									X		
Randomize Patient						X					
Dispense Study Drug						X	X	X			
Adverse Event Monitoring ⁱ						X	X	X	X		X
Concomitant Medication Monitoring						X	X	X	X		X
Study Drug Accountability							X	X	X		

^f Daily Pain Intensity Categorical Scale and VAS.

^g To be completed approximately 9 PM, two hours after evening dose.

^h Except Day 22.

ⁱ Pain Intensity Categorical Scale and VAS, and NPS.

^j See Section 9.5.1.2.1.

^a Or upon premature termination.

^b Interim history.

^c Includes orthostatic measurements at Screening Visit only.

^d Performed only if there are clinically significant abnormalities at the previous evaluation.

^e Chemistry, hematology and urinalysis.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

24

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer will instruct the patient on how to perform diary-based and site-based assessments.

Diary-based assessments include the Daily Pain Intensity Categorical Scale and the Daily Pain Intensity VAS. Each patient will receive four diaries over the course of the study. The first diary will be issued at the Screening Visit and collected at the Baseline Visit, the second will be issued at the Baseline Visit and collected at Treatment Visit I, the third will be issued at Treatment Visit I and collected at Treatment Visit II and the fourth will be issued at Treatment Visit II and collected at Treatment Visit III. Diaries will be retained at the investigative site and considered source documents. Information from the diaries will be transferred onto the appropriate CRF.

Site-based assessments include the Pain Intensity Categorical Scale, the Pain Intensity VAS, the NPS and the Patient Global Evaluation (the latter only at Treatment Visit III).

Daily Pain Intensity Categorical Scale and Daily Pain Intensity VAS

Patients will assess Pain Intensity by completing a four-point categorical scale and marking a VAS (Appendix F) in their diaries. These assessments will be completed at the same time each evening (approximately 9 PM), two hours after the evening dose of study medication. Patients will record the time they completed these assessments.

Pain Intensity Categorical Scale and Pain Intensity VAS

At the investigative site, patients will assess Pain Intensity by completing a four-point categorical scale and marking a VAS (Appendix F) at the investigative site. These assessments will be completed at the Baseline Visit (Day 1) and at Treatment Visits I, II and III (Days 8, 15 and 22). The time these assessments were performed, the time and date of a patient's prior dose of study drug will be recorded.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

25

Neuropathic Pain Scale (NPS)

The NPS (Appendix G) will be completed for patients at the Baseline Visit and at Treatment Visits I, II, and III (Days 8, 15 and 22).

Patient Global Evaluation

The Patient Global Evaluation (Appendix F) of analgesic relief due to study drug will be performed at Treatment Visit III (Day 22) or upon premature termination.

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative will explain the nature of the study to the patient and answer all questions regarding this study. Prior to any screening procedures being performed on the patient, the informed consent statement will be reviewed and signed and dated by the patient and by the person who administered the informed consent. A copy of the informed consent form will be given to the patient and a copy will be placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the patient received a signed copy.

Medical History

A complete medical history (including nicotine use) will be obtained from each patient during the Screening Visit. In addition, history of medication (prescription or OTC) use over the two weeks prior to screening will be recorded. The medical history will be updated at the Baseline Visit (Day 1).

Physical Examination

A physical examination, including weight, will be performed at the Screening Visit, Baseline Visit (Day 1), Treatment Visit III (Day 22) and at the Follow-up Visit (between Day 29 and Day 32). Height will be obtained at the Baseline Visit only. The physical examination performed at the Baseline Visit will serve as the baseline physical examination.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

26

Vital Signs

Blood pressure, pulse rate, respiration rate, and oral temperature will be measured at the Screening Visit, Baseline Visit (Day 1), Treatment Visits I, II and III (Days 8, 15 and 22) and at the Follow-up Visit (between Day 29 and Day 32). Orthostatic blood pressure will be measured at the Screening Visit. Vital sign measurements at the Baseline Visit will serve as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) should be obtained after the patient has been sitting for at least three minutes. Orthostatic measurements should be obtained after three minutes in the supine position and then after one minute in the standing position. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Patients should not wear tight sleeves. Ideally, the patient's blood pressure should be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws. Patients should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

Electrocardiogram (ECG)

A 12-lead ECG will be obtained at the Screening Visit, Baseline Visit (Day 1) and Treatment Visit III (Day 22). An ECG will be performed at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The ECG performed at the Baseline Visit will serve as the baseline ECG.

A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples will be obtained for the laboratory tests listed in Table 9.5.b at the Screening Visit, Baseline Visit (Day 1), and Treatment Visits I, II and III (Days 8, 15 and 22). Laboratory tests will be obtained at the Follow-up Visit if clinically significant

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

27

abnormalities are present on the previous evaluation. The laboratory test results obtained at the Baseline Visit will serve as the baseline results. Blood draws should be performed after pain assessments or vital sign determinations during a visit.

Table 9.5b Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
RBC count	Total bilirubin	pH
WBC count	Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)	Bilirubin
Neutrophils	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Hemoglobin A _{1c} (Baseline Visit Only)	Chloride	
Lymphocytes	Calcium	
Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)	Inorganic phosphorus	
Platelet count (estimate not acceptable)	Uric Acid	
Prothrombin Time (PT)	Bicarbonate	
Partial Thromboplastin Time (PTT)	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

28

In addition, a creatinine clearance will be calculated based upon clinical laboratory tests at the Screening Visit according to the following formula:

$$\text{MEN: CrCl (mL/min)} = \frac{\text{Ideal Body Weight (kg)} \times (140 - \text{age in yrs})}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Ideal Body Weight (Men) in kg} = 50 + (2.3 \times \text{height in inches over 5 ft})$$

WOMEN: 0.85 x value calculated for men

$$\text{Ideal Body Weight (Women) in kg} = 45.5 + (2.3 \times \text{height in inches over 5 ft})$$

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

The investigator will review all laboratory test results. For each abnormal result, the investigator will assess clinical significance and provide an etiology, if clinically significant. The assessment of etiology will use one of the following categories:

- Concurrent Medication (medication must be specified)
- Concurrent Disease (disease must be specified)
- Sample or laboratory error
- Unknown
- Non-fasting specimen (chemistry only)
- Other (must specify)

All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A copy of each laboratory report must be included with the CRF.

Viral Hepatitis Screen

Patients will undergo serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody) at the Screening Visit. The hepatitis test panel will be performed by the central laboratory.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

29

Urine Drug Screen and Alcohol Screen

Urine specimens will be tested for drugs of abuse and alcohol at the Screening Visit and will be performed by the central laboratory.

Pregnancy Test

A urine pregnancy test will be performed by designated study personnel for female patients at the Screening Visit, Baseline Visit and at Treatment Visits I, II and III (Days 8, 15 and 22). A lactating or pregnant female will not be eligible for participation in this study.

9.5.1.2.1 Adverse Events

An adverse event is defined as any unexpected and unfavorable event such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of a drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the patient.

The patient will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken and all adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the patient, will be reported on the appropriate CRF.

The investigator will assess and record any adverse event in detail on the adverse event CRF including the date and time of onset, description, severity, intermittence, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as intermittent or continuous, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

30

Table 9.5c Definitions for Investigator Rating of Adverse Event Severity

Rating	Definition
Mild	The adverse event is transient and easily tolerated by the patient.
Moderate	The adverse event causes the subject discomfort and interrupts the patient's usual activities.
Severe	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Rating	Definition
Probable	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possible	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

31

Adverse events will be monitored continuously from the time of study drug administration to the Follow-Up Visit. Only serious adverse events will be collected from the time of informed consent to study drug administration. Patients will be instructed to report to the investigator any other adverse events that occur after the Follow-up Visit.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

Since measurements of pain intensity are efficacy measurements in this study, any change in pain intensity due to the underlying pain state under study will not be considered adverse events for the purposes of this study.

9.5.1.2.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to Abbott as a serious adverse event (SAE) within 24 hours of occurrence or notification to the site:

- | | |
|--------------------------|--|
| Fatal: | An event which results in the death of a patient. |
| Life-Threatening: | An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| Hospitalization: | An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility. |

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

32

Prolongs Hospitalization:	An event which occurs while the study patient is hospitalized and that prolongs the patient's hospital stay.
Persistent or Significant Disability:	An event which results in a condition that interferes with the activities of daily living of a study patient (e.g., permanent loss of vision).
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Requires Medical or Surgical Intervention:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, spontaneous and elective abortions will be reported to Abbott Laboratories as serious adverse events.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone, one of the following people at Abbott Laboratories within 24 hours of being made aware of any SAE.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

33

Bruce G. McCarthy, M.D.
Associate Medical Director
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-3537
Office: (847) 935-6244
Home: (773) 529-5729
Fax: (847) 938-5258

Christopher J. Silber, M.D.
Venture Head
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-3537
Office: (847) 938-5236
Home: (847) 615-0428
Fax: (847) 938-5258

Fred Siebert
Sr. Clinical Research Associate
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-3537
Office: (847) 938-1167
Home: (847) 298-4682
Fax: (847) 938-5258

In addition, a written confirmation of the occurrence, including any supplementary data, must be sent within three days of the telephone report to:

Bruce G. McCarthy, M.D.
Dept. 48Q, Bldg. AP34
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-3537
Fax: (847) 938-5258

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study are standard and validated. All clinical and laboratory procedures in this study are standard and generally accepted.

9.5.3 Efficacy Variables

All efficacy variables will be derived from the efficacy measurements (section 9.5.1.1).

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

34

9.5.3.1 Primary Variable(s)

The primary efficacy variable in the study will be the change from baseline of the average Daily Pain Intensity Categorical Scale score from each patient's diary to the corresponding average of the last three days on study drug.

9.5.3.2 Secondary Variable(s)

The secondary efficacy variables include the change from baseline of the average Daily Pain Intensity VAS score from each patient's diary to the corresponding average of the last three days on the study drug, change from baseline of the pain intensity scores (categorical and VAS scores) at each visit, change from baseline to the total of the Neuropathic Pain Scale at each visit, and the Patient Global Evaluation at Treatment Visit III. The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site.

9.5.4 Blood Samples for Genetic Polymorphism Analysis

Two (2) 10 ml whole blood samples will be collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis will not be reported with the study summary. The samples may also be used for development of a diagnostic test for drug response.

The pharmacogenetic analyses involve two methods: one which examines known genes believed to be involved in the particular response (Candidate Gene), and one which uses a high density marker map to locate and identify genes related to the response (Genomic

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

35

Association) by comparing the marker profile between the patients with an effect and a corresponding negative control group. The Candidate Gene method includes genes related to drug metabolism, drug targets or target pathways, and others including genes relating to cellular homeostasis. The Genomic Association method utilizes a map of single nucleotide polymorphisms which by themselves are essentially meaningless, but when correlated with groups of two distinct patient groups allow the identification of the gene(s) related to the difference between the groups. For the purpose of pharmacogenetic studies such as this, the difference would be related to the response to the drug or the presence or absence of the disease being tested.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting will entail a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and be given a CRF completion workbook for reference. The CRAs will monitor each site every 2 to 3 weeks. At each visit, 100% source-document review will be made against the entries on the CRFs and a quality-assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All CRFs must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the CRFs for completeness and accuracy and sign and date the set of case report forms where indicated. CRFs will be reviewed periodically for completeness, legibility, and acceptability by Abbott Laboratories personnel (or their designee) and the investigator (or designee) at the study site. The investigator must agree to provide Abbott (or designee) access to all source documents in order to verify CRF entries.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

36

Data captured on the CRF will be entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF will be reviewed and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values, and any necessary corrections will be made to the database and documented via addenda or audit trail.

The laboratory results will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests will be two-tailed and considered statistically significant if the p-value (type one error rate) is less than or equal to 0.05 (when rounded to three decimal places).

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group. Appropriate secondary comparisons will be made as considered necessary.

Baseline value for all variables is defined at the last value obtained prior to receiving study drug.

9.7.1.1 Data Sets Analyzed

Efficacy analyses will be performed for two sets of data: intent-to-treat patients and evaluable patients, as defined in accordance with Sections 9.3.1 and 9.3.2. Patients receiving at least one dose of study drug with at least one baseline and one post-dose pain assessment will be included in the intent-to-treat analyses. Classification of patients regarding acceptability of data for evaluable efficacy analyses will be carried

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

37

out by the project team (clinical, data management, and statistics) prior to their knowledge of double-blind treatment assignment. Safety analyses will be performed with all randomized patients who receive at least one dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the treatment groups. Comparability among the treatment groups will be assessed by a one-way analysis of variance (ANOVA), with treatment group as the main effect for quantitative variables, and by Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

The primary efficacy variable in the study will be the change from baseline of the average Daily Pain Intensity Categorical Scale score from each patient's diary to the corresponding average of the last three days on study drug. The baseline pain score for diary data is defined as the average of the last three days of pain scores prior to dosing.

The secondary efficacy variables include the change from baseline of the average Daily Pain Intensity VAS score from each patient's diary to the corresponding average of the last three days on the study drug, change from baseline of the pain intensity scores (categorical and VAS) at each visit, change from baseline to the total of the Neuropathic Pain Scale at each visit, and the patient global Evaluation at Visit III. The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site. Change to intermediate time points will also be examined.

The change from baseline pain scores will be analyzed by using analysis of variance (ANOVA) techniques with the effects of treatment, investigator sites and the interaction between the treatment and investigator sites. Investigator sites with few patients may be combined based on geographical location prior to breaking the blind.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 4

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

38

If indicated, exploratory analyses will be performed on the change from baseline efficacy pain scores, such as analysis of covariance (ANCOVA), with baseline pain score as a covariate. If the change from baseline pain scores do not follow a normal distribution then nonparametric tests may be applied.

The final global evaluation score will be compared among the treatment groups by Cochran-Mantel-Haenszel test controlling for investigative site.

Other analyses will be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, will be performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses will use the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every patient in the analysis will have data for each specified evaluation. This technique reduces the bias caused by patients who prematurely terminate for lack of efficacy. The "observed cases" (OC) analysis will not estimate the missing evaluation, and a patient who does not have pain evaluation on a scheduled visit or day will be excluded from the OC analysis for that visit or day.

9.7.1.4 Safety

All patients receiving at least one dose of study drug will be evaluated for safety.

Adverse events will be coded using the COSTART V⁵ dictionary. Treatment-emergent adverse events (i.e., those which begin or worsen in severity after randomized study drug is taken) will be tabulated by body system and COSTART term for each treatment group. Pairwise comparisons between placebo and each treatment group will be made using Fisher's exact test for the proportion of patients reporting a particular adverse event. Analyses by subgroup will be performed as appropriate.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two – January 5, 1999

39

Laboratory data will be analyzed using a one-way ANOVA with treatment as the main effect. Baseline comparability among treatment groups will be assessed by the overall F-test of the one-way ANOVA. The primary analyses will be on the change from baseline to the final values during the study for each laboratory variable.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory results which satisfy the criteria for potentially clinically significant results (Appendix H) will be identified.

Mean changes from baseline to the final values for both vital signs and ECG will be analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfy the criteria for potentially clinically significant results (Appendix H) will be identified.

Additional safety analyses will be performed as indicated.

9.7.2 Determination of Sample Size

The study is designed to enroll approximately 150 patients (approximately 50 patients in each treatment group). This sample size allows for the detection of a 20% difference in the percentage of patients experiencing improvement between ABT-594 and placebo at 0.05 two-tailed type I error with approximately 56% power. It is expected that 25% of placebo patients will experience improvement on the global evaluation.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

This study will be conducted in accordance with the protocol, GCP, all applicable local, state federal regulations and regulatory requirements. Neither the investigator nor the CRO will modify this protocol without first obtaining the concurrence of Abbott Laboratories. The modification must be documented in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

40

patient or those of an administrative or clarifying nature, must be reviewed and approved by the Institutional Review Board before implementation. Abbott Laboratories must submit protocol amendments to the FDA and possibly to other government agencies.

This study will be terminated if these conditions are not met.

10.0 Protocol Deviations

When deviation from the protocol is deemed necessary for an individual patient, the investigator or other physician in attendance must contact the site study monitor at the CRO, who will contact Abbott Laboratories. Such contact will be made as soon as possible to permit a decision as to whether or not the patient is to continue in the study. Any departures from the protocol will be authorized only for that one patient. A description of the departure from the protocol and the reason for it will be recorded on the CRF.

11.0 Use of Information and Publication

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594**Protocol M98-833****Incorporating Amendment Nos. One and Two – January 5, 1999**

41

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 90 days before the date of submission to the intended publisher.

Neither the subject nor their physician will be informed of individual patient pharmacogenetic results, should they be performed, nor will anyone not directly involved in this research. This is due to the fact that, 1) the patient and their physician are already aware of the patient's particular response to the drug and the study information would not affect their future medical care, and 2) if an association is established between a genetic sequence and a treatment response, separate studies must be conducted in order to validate or confirm the results and the properties of the test prior to the necessary regulatory approval to use the test for diagnostic purposes. DNA samples from this protocol may be used either for gene identification, validation, or diagnostic test development studies, as well as discovery of genes related to painful polyneuropathies.

12.0 Completion of The Study

The investigator will complete and report this study in satisfactory compliance with the protocol within nine months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon in writing by both the investigator and Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are not pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

42

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

IN/R-S/1/ABT594/98833/98833AM2/P24-43
GO2Q143011

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

43

14.0 References

1. American Academy of Pain Medicine (1997). The Use of Opioids for the Treatment of Chronic Pain. pp. 1-4.
2. Twycross R. Pain Relief in Advanced Cancer. Churchill Livingstone, Edinburgh, 1994.
3. Sullivan JP and Bannon AW. Epibatidine: pharmacologic properties of a novel nicotinic acetylcholine agonist and analgesic agent. *CNS Drug Rev.* 2(1):21-39, 1996.
4. Sullivan JP, Briggs CA, Donnelly-Roberts D, Brioni JD, Radek RJ, McKenna DG, Campbell JE, Arneric SP, Decker MW, Bannon AW. (\pm)-Epibatidine can differentially evoke responses mediated by putative subtypes of nicotinic acetylcholine receptors (nAChRs). *Med Chem Res*, 4:502-516; 1994.
5. "COSTART" Coding Symbols for Thesaurus of Adverse Reaction Terms: Third Edition, Department of Health and Human Services, Food and Drug Administration, Rockville, MD, 1989.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

44

Appendix A

Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott Laboratories has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed protocol for the study.
2. A signed Form FDA 1572 or equivalent document certifying the investigator's agreement to comply with U.S. Federal (21 CFR, ICH GCP Guidelines) regulations governing the conduct of the study.
3. A current curriculum vitae of the investigator. If sub-investigators will participate in the study, a curriculum vitae for each.
4. Requirements for the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
 - A copy of the letter of approval of the IRB/IEC. The letter must specify that both the protocol and consent form were approved.
 - The names and affiliations of the members of the IRB/IEC or assurance number.
 - If the principal and/or sub-investigator is a member of the IRB/IEC, a letter stating that he/she did not participate in the review or approval of the protocol or consent form.
5. A specimen copy of the IRB/IEC-approved informed consent document to be used in the study.
6. A list of normal ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

As a rule, these documents will be provided in the course of one or more visits to the investigator by an Abbott Laboratories representative. Usually the study cannot begin until all of the documents listed above have been provided.

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

45

Appendix B

Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,
35th World Medical Assembly, Venice, Italy, in October 1983,
41st World Medical Assembly, Hong Kong, in September 1989 and
48th General Assembly, Somerset West, Republic of South Africa 1996.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

46

Appendix B (Cont.)

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

47

Appendix B (Cont.)

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obligated to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.
10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

48

Appendix B (Cont.)

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician - patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REASON FOR REVISION: Revised to correspond to the amendment adopted by the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa 1996.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

49

Appendix C

Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott Laboratories are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is actually a form letter addressed to the sponsor (Abbott Laboratories), summarizing the investigators qualifications for the study and their willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. To secure prior approval of the study by an appropriate institutional review board which conforms to FDA regulations.
2. To make at least yearly reports on the progress of the study to the above committee, and a final report within three months of study completion.
3. To maintain current running records of the receipt, administration, and disposition of study medication and to return all unused study medication to Abbott Laboratories.
4. To obtain valid written informed consent from each patient who participates in the study.
5. To prepare and maintain adequate case histories of all persons entered into the study, including case report forms, hospital records, laboratory results, etc., and to maintain these data for a minimum of two years following notification by Abbott Laboratories that all investigations have been discontinued with this drug.
6. To identify all subinvestigators who will also supervise drug administration.
7. To report adverse effects to Abbott Laboratories promptly. In the event of serious or unexpected adverse event, to notify Abbott Laboratories immediately by telephone.
8. To allow possible inspection and copying by the FDA of case reports and records of drug distribution.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

50

Appendix D

Elements of the Consent Form

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

For IND Studies, procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all patients participating in PPD Clinical Research studies or the patients' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of patients involved in the trial.
4. The expected duration of the patient's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The patient's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the patient and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the patient for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the patient, this should be stated.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

51

Appendix D (Cont.)

13. The anticipated prorated payment, if any, to the patient for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
15. A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research patient's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the patient.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the patients' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the patient or the patient's legally acceptable representative is authorizing such access.
21. A statement that the site will collect information on the patient per ICH requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency will also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site.
22. A statement that the records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the patients' participation in the trial may be terminated.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

52

Appendix D (Cont.)

- 24. Procedures for orderly termination of participation.**
- 25. A statement that participation is voluntary.**
- 26. A statement that refusal to participate will involve no penalty or loss of benefits.**
- 27. A statement that the patient may discontinue participation at any time without penalty or loss of benefits.**
- 28. A statement that a signed and dated copy of the consent is given to the patient.**
- 29. The statement, "I agree to participate..."**
- 30. A place for the patient or the patient's legally acceptable representative to sign and date.**
- 31. A place for the person who conducted the informed consent discussion to sign and date.**

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

53

Appendix E

Sample Abbott Laboratories Drug Accountability Form

Date Received (M/D/Y)	Clinical Supplies Invoice No.	No. of Medication Containers Received
/ /		
/ /		

Study M98-833

NPRO #: _____

Investigator's Name: _____

Location: _____

Patient Number: _____

Patient Initials: _____

Visit	DISPENSED TO PATIENT			RETURNED FROM PATIENT			VERIFIED BY CRA	
	Bottle #	# SEC	Date	By*	Date	No. of SEC Remaining	By*	Date
Baseline	A	20						
	B	20						
Visit I	A	20						
	B	20						
Visit II	A	20						
	B	20						

* Pharmacist/Coordinator/Nurse
 + CRO monitor

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 5

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two – January 5, 1999

54

Appendix F

Pain Assessments

The time and date of every pain assessment will be recorded.

The patient should be reminded that each assessment should be performed independently of previous assessments.

Daily Pain Intensity Categorical Scale

The patient's pain intensity will be assessed by completion of the following statement in the patient's diary.

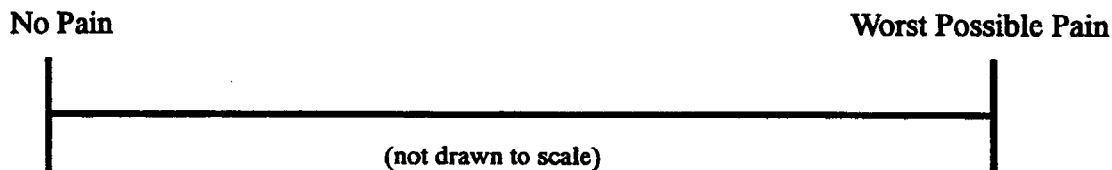
How severe was your neuropathy pain during the last 24 hours?

- | | |
|---|----------|
| 0 | None |
| 1 | Mild |
| 2 | Moderate |
| 3 | Severe |

Daily Pain Intensity Visual Analog Scale (VAS)

The patient will place a line on the VAS in the diary to indicate the magnitude of his/her pain.

How severe was your neuropathy pain during the last 24 hours?



Using a standard ruler supplied by Abbott, site personnel will measure the distance in millimeters (0–100 mm) from the left side of the scale to the patient's vertical mark and record this number on the appropriate CRF page.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

55

Appendix F (Cont.)

Pain Intensity Categorical Scale

The patient's pain intensity will be assessed by completion of the following statement at the investigative site.

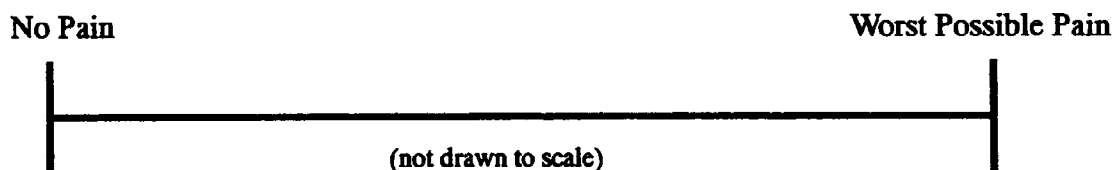
How severe was your neuropathy pain during the last 24 hours?

- 0 None
- 1 Mild
- 2 Moderate
- 3 Severe

Pain Intensity VAS

The patient will place a line on the VAS in the patient pain assessment worksheet to indicate the magnitude of his/her pain at the investigative site.

How severe was your neuropathy pain during the last 24 hours?



Using a standard ruler, site personnel will measure the distance in millimeters (0-100 mm) from the left side of the scale to the patient's vertical mark and record this number on the appropriate CRF page.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M98-833
Incorporating Amendment Nos. One and Two - January 5, 1999

56

Appendix F (Cont.)

Patient Global Evaluation

The patient's overall impression of the study drug will be assessed by completion of the following statement:

How would you rate the study medication?

- 4 Excellent
- 3 Good
- 2 Fair
- 1 Poor

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

57

Appendix G

Neuropathic Pain Scale

Instructions: There are several different aspects of pain which we are interested in measuring: pain sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface vs. deep pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how intense your pain is. Place an "X" through the number that best describes the intensity of your pain.												
No pain	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most intense pain sensation imaginable											
2. Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."												
Not sharp	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most sharp sensation imaginable ("like a knife")											
3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."												
Not hot	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most hot sensation imaginable ("on fire")											
4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."												
Not dull	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most dull sensation imaginable											

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

58

Appendix G (Cont.)

<p>5. Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include "like ice," and "freezing."</p>													
<p>Not cold</p>	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	<p>The most cold sensation imaginable ("freezing")</p>
0	1	2	3	4	5	6	7	8	9	10			
<p>6. Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."</p>													
<p>Not sensitive</p>	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	<p>The most sensitive sensation imaginable ("raw skin")</p>
0	1	2	3	4	5	6	7	8	9	10			
<p>7. Please use the scale below to tell us how itchy your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."</p>													
<p>Not itchy</p>	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	<p>The most itchy sensation imaginable ("like poison oak")</p>
0	1	2	3	4	5	6	7	8	9	10			
<p>8. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.</p>													
<p>Not unpleasant</p>	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	<p>The most unpleasant sensation imaginable ("intolerable")</p>
0	1	2	3	4	5	6	7	8	9	10			
<p>9. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.</p>													
<p>HOW INTENSE IS YOUR DEEP PAIN?</p>													
<p>No deep pain</p>	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	<p>The most intense deep pain sensation imaginable</p>
0	1	2	3	4	5	6	7	8	9	10			
<p>10. HOW INTENSE IS YOUR SURFACE PAIN?</p>													
<p>No surface pain</p>	<table border="1" style="display: inline-table; text-align: center; width: 400px;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10	<p>The most intense surface pain sensation imaginable</p>
0	1	2	3	4	5	6	7	8	9	10			

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

59

Appendix H

Potentially Clinically Significant Values for Laboratory Determinations, Vital Signs and Electrocardiogram Variables

Hematology	Very Low	Very High
Hemoglobin (g/dL)		
Female	≤ 9.5	≥ 16.5
Male	≤ 11.5	≥ 18.5
Hematocrit (%)		
Female	≤ 32	≥ 50
Male	≤ 37	≥ 55
Red Blood Cells ($\times 10^{12}/L$)		
Female	≤ 3.5	≥ 6.0
Male	≤ 3.8	≥ 7.0
White Blood Cells ($\times 10^9/L$)	≤ 2.8	≥ 16.0
Platelet Count ($\times 10^9/L$)	≤ 75	≥ 700
Eosinophils (%)		≥ 10
Basophils (%)		≥ 10
Lymphocytes (%)		≥ 75
Monocytes (%)		≥ 15
Neutrophils (%)	≤ 15	
Bands (%)		≥ 10
Mean Corpuscular Volume (fL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Mean Corpuscular Hemoglobin Concentration (g/dL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Atypical Lymphocytes (%)		≥ 5
Prothrombin Time (sec)		$\geq 2 \text{ ULN}$
Partial Thromboplastin Time (sec)		$\geq 2 \text{ ULN}$

LLN = Lower limit of normal ULN = Upper limit of normal

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

60

Appendix H (Cont.)

Chemistry	Very Low	Very High
Albumin (g/dL)	≤ 2.5	
Alkaline Phosphatase (IU/L)		$\geq 3 \times \text{ULN}$
Bicarbonate (mEq/L)	≤ 12	≥ 38
BUN (mg/dL)		≥ 30
Calcium (mg/dL)	≤ 8.2	≥ 12
Chloride (mEq/L)	≤ 90	≥ 118
Cholesterol (mg/dL)		≥ 600
Creatinine (mg/dL)		≥ 2.0
Direct Bilirubin (mg/dL)		≥ 2.0
Glucose (mg/dL)	≤ 45	≥ 175
LDH (IU/L)		$\geq 3 \times \text{ULN}$
Inorganic Phosphorus (mg/dL)	≤ 1.7	≥ 5.5
Potassium (mEq/L)	≤ 3.0	≥ 6.0
SGOT/AST (IU/L)		$\geq 3 \times \text{ULN}$
SGPT/ALT (IU/L)		$\geq 3 \times \text{ULN}$
Sodium (mEq/L)	≤ 126	≥ 156
Total Bilirubin (mg/dL)		≥ 2.0
Total Protein (g/dL)	≤ 4.5	≥ 10
Triglycerides (mg/dL)		≥ 600
Uric acid (mg/dL)		
Female		≥ 8.5
Male		≥ 10.5

ULN = Upper limit of normal

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M98-833

Incorporating Amendment Nos. One and Two - January 5, 1999

61

Appendix H (Cont.)

Urinalysis	Very Low	Very High
Specific Gravity	≤ 1.001	≥ 1.030
PH	≤ 4	≥ 9
Protein		$\geq 3+^* (\geq 10)$
Ketones		$\geq 3+^*$
RBC		
Female		$\geq 10/\text{hpf}$
Male		$\geq 8/\text{hpf}$
WBC		$\geq 10/\text{hpf} (\geq 2+)$
Casts		≥ 9
Glucose		$\geq 3+^*$
Oral Body Temperature		
Temperature	Low: decreased $\geq 2^\circ\text{F}$ from baseline	
	High: $\geq 101^\circ\text{F}$ and increased $\geq 2^\circ\text{F}$ from baseline	
Body Weight		
Weight	Low: decreased $\geq 15\%$ from baseline	
	High: increased $\geq 15\%$ from baseline	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mmHg and decreased ≥ 30 from baseline	
	High: ≥ 180 mmHg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mmHg and decreased ≥ 20 from baseline	
	High: ≥ 105 mmHg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline	
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	
Orthostatic Vital Signs		
Systolic Blood Pressure	Low: ≤ 86 mmHg and decreased ≥ 30 from supine	
Heart rate	High: ≥ 130 bpm and increased ≥ 20 bpm from supine	

* $\geq 3+$ on a scale with 4+ being the maximum valueCONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M98-833
 Incorporating Amendment Nos. One and Two - January 5, 1999

62

Appendix H (Cont.)

Electrocardiogram	
PR Interval	High: ≥ 210 msec
QRS Duration	Low: ≤ 50 msec
	High: ≥ 150 msec
QT Interval	Low: ≤ 200 msec
	High: ≥ 500 msec
QTc Interval*	Low: ≤ 200 msec
	High: ≥ 500 msec
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline

* QTc calculated as QT divided by the square root of RR interval

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.


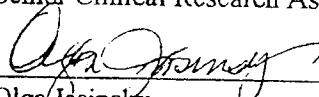
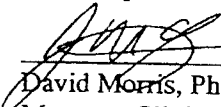
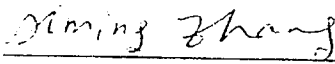
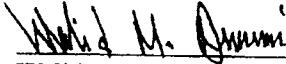

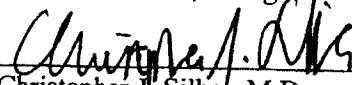
6668F2

Part 1

**ABBOTT LABORATORIES
CLINICAL PROTOCOL
INVESTIGATIONAL NEW DRUG
ABT-594
PROTOCOL M97-772**

**A Randomized, Double-Blind, Single Dose Comparison of an Oral
Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental
Pain Model**

Incorporating Amendments One and Two - June 22, 1998

 for RENE S. REITMAYER Renee S. Reitmayer Senior Clinical Research Associate, Analgesia Venture	<u>6/23/98</u> Date
 Olga Jasinsky Senior Operations Manager, Analgesia Venture	<u>6/23/98</u> Date
 for David Morris David Morris, Ph.D. Manager, Clinical Statistics	<u>6/23/98</u> Date
 for Charles Locke Charles Locke, Ph.D. Associate Research Fellow, Clinical Statistics	<u>6/23/98</u> Date
 Walid M. Awni, Ph.D. Manager, Clinical Pharmacokinetics and Toxicokinetics	<u>6/23/98</u> Date
 Rita Driscoll, M.D. Medical Director, Analgesia Venture	<u>06/24/98</u> Date
 Christopher J. Silber, M.D. Venture Head, Analgesia Venture	<u>6/23/98</u> Date

 **Abbott Laboratories**

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABBOTT LABORATORIES
CLINICAL PROTOCOL
INVESTIGATIONAL NEW DRUG
ABT-594
PROTOCOL M97-772

**A Randomized, Double-Blind, Single Dose Comparison of an Oral
Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental
Pain Model**

Amendment Two - June 22, 1998

The purpose of this amendment is to:

- include pain assessments at 12 and 24 hours after study drug administration, with changes to the study design description and planned analyses relative to these additional assessments.
- clarify the timeframe in which adverse events will be collected in this study (i.e., all adverse events from the time of study drug randomization until the Follow-up Visit and any adverse event spontaneously reported within 30 days of study drug administration will be collected).
- delineate anticipated peri-operative events following third molar extraction surgery. These peri-operative events will not be captured as adverse events in this study, unless the peri-operative event is of a greater degree than routinely associated with molar extraction surgery.

The specific changes are the following:

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Amendment Two - June 22, 1998

2

1. Study Synopsis: Methodology (cont.): 1st Paragraph

Change:

Patients will receive . . . over a period of six hours.

To:

Patients will receive . . . over a period of 24 hours.

2. Section 4.0: List of Abbreviations and Definition of Terms, Definition of Terms

Change:

SPID Time-weighted sum of pain intensity differences

SPRID Time-weighted sum of pain relief differences

To:

SPID The time-weighted sum of pain intensity differences

SPRID The time-interval-weighted sum of pain relief differences

3. Section 9.1: Overall Study Design and Plan: Description, 6th Paragraph

Change:

. . . performed at 0.25 (15 minutes), 0.50 (30 minutes), 0.75 (45 minutes), 1, 1.5, 2, 3, 4, 5, and 6 hours . . .

To:

. . . performed at 0.25 (15 minutes), 0.50 (30 minutes), 0.75 (45 minutes), 1, 1.5, 2, 3, 4, 5, 6, 12, and 24 hours . . .

4. Section 9.3.3: Removal of Patients from Therapy or Assessment, 2nd Paragraph

Change:

If a patient . . . within six hours . . . VAS, the five-point Pain Relief Categorical Scale, and a patient global evaluation of analgesic relief from study drug should be performed at the time of termination or prior to receiving rescue medication. . . .

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Amendment Two - June 22, 1998

3

To:

If a patient . . . within 24 hours . . . VAS, and the five-point Pain Relief Categorical Scale should be performed at the time of termination or prior to receiving rescue medication. For those patients who prematurely terminate or receive analgesic rescue medication within six hours of study drug administration, the patient global evaluation of analgesic relief due to study drug should also be performed at the time of termination or prior to receiving rescue medication. . . .

5. Table 9.5.A: Study Flow Chart

Change: Study Confinement Period procedure (at 6, 12 and 24 hours after dosing):

Pain Assessments (Appendix C)	• ^f		
-------------------------------	----------------	--	--

To:

Pain Assessments (Appendix C)	•	•	• ^k
-------------------------------	---	---	----------------

Change: Footnote f.

- ^f. At the last hourly observation or upon premature termination or immediately prior to receiving rescue medication (if the latter two events occur less than 6 hours post-study drug administration).

To:

- ^f. A Patient Global Evaluation will be completed at 6 hours or upon premature termination or immediately prior to receiving rescue medication, if the latter two events occur less than 6 hours post-study drug administration.

Add: New Footnote k.

- ^k. At the last hourly observation or upon premature termination or immediately prior to receiving rescue medication, if the latter two events occur less than 24 hours post-study drug administration.

6. Section 9.5.1.11: Adverse Event Monitoring

Change:

Adverse events will be continuously monitored throughout the study including the interval between the Screening Visit and the Study Confinement Period and for 30 days following study drug administration.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Amendment Two - June 22, 1998

4

To:

Adverse events will be continuously monitored throughout the study from the time of study randomization through the Follow-up Visit (five to nine days after study drug administration). Adverse events which are spontaneously reported to the investigative site within 30 days following study drug administration will also be captured.

7. Section 9.5.2: Efficacy Procedures, Last Paragraph

Change:

... within 6 hours of study drug ... VAS, the five-point Pain Categorical Scale, and the patient global evaluation of analgesic relief due to study drug will be ...

To:

... within 24 hours of study drug ... VAS, and the five-point Pain Relief Categorical Scale will be ...

Add:

For those patients who prematurely terminate or receive analgesic rescue medications within six hours of study drug administration, the patient global evaluation of analgesic relief due to study drug should also be performed at the time of termination or prior to receiving rescue medication.

8. Section 9.5.2.1: Pain Intensity Categorical Scale and Pain Intensity Visual Analog Scale (VAS), Last Paragraph

Change:

... 4, 5, and 6 hours ...

To:

... 4, 5, 6, 12 and 24 hours ...

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Amendment Two - June 22, 1998

5

9. Section 9.5.2.2: Pain Relief Categorical Scale and Stop Watch Method, Last Paragraph

Change:

... 4, 5, and 6 hours ...

To:

... 4, 5, 6, 12 and 24 hours ...

10. Section 9.5.3.1: Collection and Storage of Blood Samples for ABT-594 Plasma Assay, First Paragraph

Change:

... into a heparinized evacuated ...

To:

... into a sodium heparinized evacuated ...

11. Section 9.5.4.1: Adverse Events, 1st Paragraph

Change:

... after the informed consent is signed.

To:

... after study randomization in this study.

12. Section 9.5.4.1: Adverse Events, Last Paragraph

Add:

In addition, anticipated peri-operative events following molar extraction surgery, such as swelling or edema, hematoma, bleeding, dry socket, nerve injury, oral-antral communication (sinus exposure), infection, decrease in mandibular range of motion, soreness with mandibular movement, and bruising, will not be captured as adverse events

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Amendment Two - June 22, 1998

6

in this study. If, in the opinion of the investigator, the peri-operative event is of a greater degree than routinely associated with molar extraction surgery, then the event will be recorded as an adverse event.

13. Section 9.5.4.2: Serious Adverse Events

Change: Address List

Bruce McCarthy, M. D.
Office: (847) 935-56244

To:

Bruce McCarthy, M.D.
Office: (847) 935-6244

14. Section 9.5.6: Primary Efficacy Variables and Criteria for Evaluability

Add:

All the time-interval-weighted pain scores (TOTPAR, SPID, SPRID) will be calculated through the first six hours after study drug administration. The time to the patient's first noticeable pain relief and first meaningful pain relief will be measured through the first six hours of study drug administration while the time to rescue medication will be recorded through the first 24 hours after study drug administration.

15. Section 9.7.1: Statistical and Analytical Plans, 1st Paragraph, Last Sentence

Delete:

All analyses will be performed using SAS®.

16. Section 9.7.1.3: Efficacy Analyses, 2nd Paragraph

Change:

For the efficacy variables measuring time to an event, (e.g., time to experiencing meaningful pain relief), patients who do not report the event within six hours after dosing will be considered censored at six hours.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Amendment Two - June 22, 1998

7

To:

The secondary efficacy variables, time to first noticeable pain relief and first meaningful pain relief, within six hours after dosing will be considered censored at six hours and time to rescue medication will be censored at 24 hours. The information obtained from the pain assessments completed at 12 and 24 hours after study drug administration will be collected for informational purposes and utilized for the development of future study designs.

17. Section 9.7.1.3: Efficacy Analyses, 3rd Paragraph

Add: to beginning of paragraph

The time-interval-weighted pain scores will be calculated through the first six hours after study drug administration.

18. Appendix C: Pain Assessments, 1st Paragraph

Change:

. . . recorded at each time point as specified in Section 9.5.2.

To:

. . . recorded at the time points specified in Section 9.5.2.

19. Appendix C: Pain Assessments, Under Patient Global Evaluation, 1st Sentence

Change:

At the last hourly observation period or upon . . .

To:

At 6 hours after study drug administration or upon . . .

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Amendment Two - June 22, 1998

8

20. Appendix C: Pain Assessments, Under Patient Global Evaluation,
1st Sentence

Change:

At the last hourly observation period or upon . . .

To:

At 6 hours after study drug administration or upon . . .

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

1.0 Title Page

ABBOTT LABORATORIES CLINICAL PROTOCOL INVESTIGATIONAL NEW DRUG

ABT-594 PROTOCOL M97-772

A Randomized, Double-Blind, Single Dose Comparison of an Oral Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental Pain Model

Incorporating Amendments One and Two - June 22, 1998

Part or all of the information in this protocol may be unpublished material. Accordingly, this protocol is to be treated as confidential, and restricted to its intended use. Should any portion of this unpublished material be desired for purposes of publication, authorization is to be obtained from Abbott Laboratories.

 **Abbott Laboratories**

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two – June 22, 1998

2

2.0 Table of Contents

	Page
1.0 Title Page	1
2.0 Table of Contents	2
3.0 Study Synopsis	7
4.0 List of Abbreviations and Definition of Terms	10
5.0 Ethics	13
5.1 Institutional Review Board	13
5.2 Ethical Conduct of the Study	13
5.3 Patient Information and Consent	13
5.4 Patient Confidentiality	14
6.0 Investigator and Study Administrative Structure	14
6.1 Investigative Site	14
6.2 Sponsor Information	15
6.3 Clinical Supply Management	15
6.4 Central Laboratories	15
6.5 Administrative Structure	16
7.0 Introduction	17
8.0 Study Objective	20
9.0 Investigational Plan	21
9.1 Overall Study Design and Plan: Description	21
9.2 Discussion of Study Design	24
9.3 Selection of Study Population	25
9.3.1 Inclusion Criteria	25
9.3.2 Exclusion Criteria	26
9.3.3 Removal of Patients from Therapy or Assessment	28
9.4 Treatments	29

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

3

Table of Contents (Continued)

	Page
9.4.1 Treatments Administered	29
9.4.2 Identity of Investigational Products	31
9.4.2.1 Packaging and Labeling	31
9.4.2.2 Study Medication Preparation	32
9.4.2.3 Storage and Disposition of Supplies	33
9.4.3 Method of Assigning Patients to Treatment Groups	33
9.4.4 Selection of Doses in the Study	34
9.4.5 Selection and Timing of Dose for Each Patient	34
9.4.6 Blinding	35
9.4.7 Prior and Concomitant Medication	36
9.4.8 Treatment Compliance	36
9.4.9 Drug Accountability	36
9.5 Efficacy, Pharmacokinetic, and Safety Variables	37
9.5.1 Efficacy, Pharmacokinetic, and Safety Measurements to be Assessed and Flow Chart	37
9.5.1.1 Informed Consent	39
9.5.1.2 Medical History (including nicotine product use)	39
9.5.1.3 Physical Examination	39
9.5.1.4 Vital Signs	40
9.5.1.5 Electrocardiogram (ECG)	40
9.5.1.6 Clinical Laboratory Testing	40
9.5.1.7 Hepatitis Screen	42
9.5.1.8 Urine Drug Screen and Breath Alcohol Screen	42
9.5.1.9 Serum Cotinine	42

CONFIDENTIAL INFORMATION ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

4

Table of Contents

(Continued)

	Page
9.5.1.10 Pregnancy Test	43
9.5.1.11 Adverse Event Monitoring	43
9.5.1.12 Pharmacokinetic Sampling	43
9.5.2 Efficacy Procedures	44
9.5.2.1 Pain Intensity Categorical Scale and Pain Intensity Visual Analog Scale (VAS)	44
9.5.2.2 Pain Relief Categorical Scale and Stop Watch Method	45
9.5.2.3 Patient Global Evaluation	45
9.5.2.4 Analgesic Rescue Medication Use	46
9.5.3 Pharmacokinetic Procedures (Drug Concentration Measurements)	46
9.5.3.1 Collection and Storage of Blood Samples for ABT-594 Plasma Assay	46
9.5.3.2 Shipment of Plasma Samples	47
9.5.4 Safety Procedures	48
9.5.4.1 Adverse Events	48
9.5.4.2 Serious Adverse Events	50
9.5.5 Appropriateness of Measurement	51
9.5.6 Primary Efficacy Variables and Criteria for Evaluability	51
9.5.7 Drug Concentration Variables	52
9.6 Data Quality Assurance	52
9.7 Statistical Methods and Determination of Sample Size	53
9.7.1 Statistical and Analytical Plans	53
9.7.1.1 Data Sets Analyzed	53
9.7.1.2 Demographic and Other Baseline Characteristics	54

CONFIDENTIAL INFORMATION ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

5

Table of Contents (Continued)

	Page
9.7.1.3 Efficacy Analyses	54
9.7.1.4 Safety	55
9.7.1.5 Pharmacokinetics	56
9.7.2 Determination of Sample Size	57
9.8 Changes in the Conduct of the Study or Planned Analyses	57
9.8.1 Changes in the Conduct of the Study	57
10.0 Protocol Deviation	58
11.0 Use of Information and Publication	58
12.0 Completion of the Study	58
13.0 Investigator's Agreement	60
14.0 References	61

List of Appendices

Appendix A Responsibilities of the Clinical Investigator	62
Appendix B Elements of an Informed Consent	63
Appendix C Pain Assessments	66
Appendix D Instructions for the Collection and Handling of Blood Samples	69
Appendix E Potentially Clinically Significant Values for Laboratory Determinations, Vital Signs and Electrocardiogram Variables	70

List of Attachments

Attachment I Sample Abbott Laboratories Drug Inventory Form	74
---	----

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

6

Table of Contents **(Continued)**

Page

List of Figures

Figure 6.5A: Administrative Structure	16
Figure 9.1A: Study Design	23

List of Tables

Table 9.1A: Dosing Segments	24
Table 9.4A: Study Drug Administration	30
Table 9.4B: Identification of Test Preparations	31
Table 9.5A: Study Flow Chart	38
Table 9.5B: Clinical Laboratory Tests	41

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

7

3.0 Study Synopsis

Name of Company: Abbott Laboratories	Individual Study Table Refer- ring to Item of the Submission: N/A	(For National Authority Use Only)
Name of Finished Product: ABT-594 Powder for Oral Solution, 50.5 mg (Base Equivalents) per Bottle	Volume: N/A	
Name of Active Ingredient: ABT-594	Page: N/A	
Title of Study:	A Randomized, Double-Blind, Single Dose Comparison of an Oral Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental Pain Model	
Investigator: Dr. Stephen Daniels	Investigative Site: SCIREX Corporation 1305 Wonder World Drive, Suite #202 San Marcos, TX 78666	
Publication (reference): N/A		
Study Period (years): Estimated Date of First Enrollment: July, 1998 Estimated Date of Last Enrollment: October, 1998	Stage of Development: Phase II	
Objective: <p>The objective of this study is to assess the safety and efficacy of single dose administration of four different doses of an oral solution of ABT-594 as compared to ibuprofen 400 mg and placebo, and to evaluate the pharmacokinetics of ABT-594 in patients after third molar extraction surgery.</p>		
Methodology: <p>This is a Phase II, randomized, parallel group, double-blind, placebo-controlled study to be conducted at a single investigative site in the United States. It is anticipated that approximately 288 patients will be randomized over the estimated four-month study period.</p> <p>The study will consist of a Screening Visit in the fourteen days prior to surgery, a Study Confinement Period consisting of third molar extraction surgery, study drug administration, and subsequent study assessments, and a Follow-up Visit five to nine days after study drug administration.</p> <p>Prior to surgery, patients will be evaluated via medical history (including use of nicotine products), physical examination with vital signs, laboratory and electrocardiographic assessments, and screening for hepatitis, drugs of abuse, ethanol and nicotine product use, and, if female, pregnancy. Adult patients between the ages of 18 and 55, inclusive, with at least moderate pain severity within six hours following surgical extraction of two or more impacted third molar teeth and meeting all other study selection criteria will be eligible for study participation. Approximately 288 patients will be randomly assigned in equal numbers to six treatment groups with approximately 48 patients per group. Each treatment group will be stratified by patient nicotine use in a 2:1 ratio of non-users (n=32) to users (n=16) of nicotine products. Patients will be categorized as nicotine users (i.e., regular, daily use of nicotine products) or non-users (i.e., no nicotine product use for at least six months prior to surgery) based on patient history of nicotine product use and verified by serum cotinine level at screening.</p>		

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

8

Name of Company: Abbott Laboratories	Individual Study Table Refer- ring to Item of the Submission: N/A	<i>(For National Authority Use Only)</i>
Name of Finished Product: ABT-594 Powder for Oral Solution, 50.5 mg (Base Equivalents) per Bottle	Volume: N/A	
Name of Active Ingredient: ABT-594	Page: N/A	
Methodology (cont.): <p>Patients will receive a single dose of either one of four different doses of ABT-594, ibuprofen 400 mg, or placebo. After study drug administration, patients will undergo assessment of pain intensity, pain relief, and study drug analgesic efficacy at specified intervals over a period of 24 hours. Approximately one-half of all patients will also be assigned to have blood samples collected at specified intervals for pharmacokinetic analysis.</p> <p>Patients will be confined for 24 hours after study drug administration. Prior to release from the investigative site, patients will have clinical, laboratory, and electrocardiographic assessments performed. Patients will return five to nine days later for a follow-up assessment.</p> <p>Dosing will occur in two separate segments. Each segment will contain 144 patients. In each segment, there will be a 2:1 ratio of nicotine non-users (NIC-) to nicotine users (NIC+) within each treatment group. In each segment, 24 patients will be randomized to placebo (16 NIC-, 8 NIC+ patients), 24 patients will be randomized to ibuprofen 400 mg (16 NIC-, 8 NIC+ patients), 48 patients will be randomized to a lower dose of ABT-594 (32 NIC-, 16 NIC+ patients), and 48 patients will be randomized to a higher dose of ABT-594 (32 NIC-, 16 NIC+ patients) as specified in Table 9.1A. After the first dosing segment is completed, a blinded safety assessment will be performed, with possible adjustment of dose, prior to proceeding to the next segment.</p>		
Main Criteria for Inclusion: <p>Males and nonlactating, nonpregnant females between the ages of 18 and 55, inclusive, who are judged to be in good health based on medical history and physical examination with vital signs, laboratory profile and 12-lead electrocardiogram (ECG), with at least moderate pain severity within six hours after surgical extraction of two or more impacted third molar teeth, and meeting all other selection criteria specified in Section 9.3 will be eligible for study participation.</p>		
Test Products: ABT-594 Powder for Oral Solution, 50.5 mg (Base Equivalents) per Bottle to be reconstituted with Sterile Water for Injection [United States Pharmacopeia (USP)], to provide a final 10 µg/ml base equivalent solution Sterile Water for Injection, USP, to be utilized as a placebo oral solution to match ABT-594 oral solution Encapsulated ibuprofen 200 mg tablets Placebo capsules to match ibuprofen capsules Doses: ABT-594 25 µg, ABT-594 50 µg, ABT-594 75 µg, ABT-594 100 µg, ibuprofen 400 mg, placebo Mode of Administration: oral		

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

9

Name of Company: Abbott Laboratories	Individual Study Table Referring to Item of the Submission: N/A	<i>(For National Authority Use Only)</i>
Name of Finished Product: ABT-594 Powder for Oral Solution, 50.5 mg (Base Equivalents) per Bottle	Volume: N/A	
Name of Active Ingredient: ABT-594	Page: N/A	
Batch Numbers:		Drug Product
<u>Test Preparation</u>		<u>Lot Number</u>
ABT-594 Powder for Oral Solution, 50.5 mg (Base Equivalents) per Bottle		40-921-AR-01
Sterile Water for Injection, USP, to be used as placebo to match ABT-594 oral solution		To Be Determined
Ibuprofen 200 mg capsules		31-782-AR-03
Placebo capsules to match ibuprofen capsules		86-591-AR
Efficacy Variables: Efficacy will be assessed by determinations of pain intensity, pain relief and a patient global evaluation. These assessments include a four-point categorical scale and visual analog scale (VAS) of pain intensity, a five-point categorical scale of pain relief from baseline, and a patient global evaluation of analgesic relief due to study drug. Additionally, the time to first noticeable pain relief (i.e., onset of pain relief) and the time to first meaningful pain relief (i.e., 50% reduction in pain from baseline) will be determined via the stopwatch methodology.		
Pharmacokinetic Variables: Pharmacokinetic variables will be maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) determined by noncompartmental methods.		
Safety Variables: Safety and tolerability will be assessed by adverse event monitoring and clinical, laboratory and electrocardiographic assessments.		
Statistical Methods: Statistical Methods are presented in Section 9.7.		

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

10

4.0 List of Abbreviations and Definition of Terms

List of Abbreviations

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine]
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
ANOVA	Analysis of variance
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
bpm	Beats per minute
BUN	Blood urea nitrogen
°C	Degrees Centigrade
CFR	Code of Federal Regulations
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRA	Clinical Research Associate
CrCl	Creatinine clearance
CRF	Case Report Form
ECG	Electrocardiogram
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
fl	femtoliter (10 ⁻¹⁵ liter)
g/dl	Grams per deciliter
GCP	Good Clinical Practice
HAAb	Hepatitis A antibody
HBsAg	Hepatitis B surface antigen
HCG	Beta-human chorionic gonadotropin
HCVAb	Hepatitis C virus antibody
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
hrs	hours
hpf	high power field
ICH	International Conference on Harmonization
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IU/L	International units per liter
kg	Kilogram

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

11

4.0 List of Abbreviations and Definition of Terms (continued)

List of Abbreviations (continued)

LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LLN	Lower limit of normal of reference range for laboratory values
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
µg	Micrograms
µg/mL	Micrograms per milliliter
mEq/L	Milliequivalents per liter
mg	Milligrams
mg/dl	Milligrams per deciliter
mg/kg	Milligrams per kilogram
mg/mL	Milligrams per milliliter
mL	Milliliter
mL/min	Milliliters per minute
mm	Millimeter
mm Hg	Millimeters of mercury
msec	Milliseconds
nAChR	Nicotinic acetylcholine receptor
No.	Number
NPRO	New Product Research Order
NSAID	Nonsteroidal anti-inflammatory drugs
PI	Pain Intensity, as measured by Pain Assessments in Appendix C
PR	Pain Relief, as measured by Pain Assessments in Appendix C
PPD	Pharmaceutical Products Division, Abbott Laboratories
PT	Prothrombin time
pts	Patients
PTT	Partial thromboplastin time
RBC	Red blood cell
sec	Seconds

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

12

4.0 List of Abbreviations and Definition of Terms (continued)

List of Abbreviations (continued)

SAE	Serious Adverse Event
SAM	Shipping Account Memorandum
TCA	Tricyclic antidepressant
ULN	Upper limit of normal of reference range for laboratory values
US	United States
USP	United States Pharmacopeia
VAS	Visual Analog Scale for measurement of pain intensity
VLDL	Very low density lipoprotein
WBC	White blood cell
yrs	Years

Definition of Terms

AUC	Area under the plasma concentration-time curve
C _{max}	Maximum observed concentration
NIC+	Regular nicotine user
NIC-	Nicotine non-user
NOMAD®	A validated data management system
PID	Pain intensity difference
SAS®	A statistical software package
SPID	The time-weighted sum of pain intensity differences
SPRID	The time-weighted sum of pain relief differences
TOTPAR	The time-interval-weighted sum of pain relief scores

CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

13

5.0 Ethics

5.1 Institutional Review Board

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e. g., Institutional Review Board [IRB], Independent Ethics committee [IEC]), prior to participation of human patients in research. The investigator will obtain a duly constituted IRB review and approval of the protocol, informed consent form and all other forms of patient information related to the study (e. g., advertisements used to recruit patients). Abbott Laboratories will receive documentation of the study approval, including the signed signature page from the study protocol, patient informed consent document, and any study-related advertising as well as a list of members of the committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the sites. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, GCP, the Food and Drug Administration's (FDA) regulations governing clinical study conduct, and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix A.

5.3 Patient Information and Consent

The investigator or his/her representative will explain the nature of the study to the patient, and answer all questions regarding this study. Prior to any screening procedures being performed on the patient, the informed consent statement will be reviewed and signed and dated by the patient and the person who administered the informed consent. A copy of the informed consent form will be given to the patient and a copy will be placed in the patient's medical record. An entry must also be made in the patient's dated

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

14

source documents to confirm that informed consent was obtained prior to any study-related procedures and that the patient received a signed copy. The Responsibilities of the Investigator and the Elements of an Informed Consent are specified in Appendix A and Appendix B, respectively.

5.4 Patient Confidentiality

All reports and communications relating to patients in the study will identify each patient only by the patient's initials (first, middle, last) and by the patient's study number. However, the investigator agrees to furnish Abbott Laboratories with complete patient identification on the Confidential Patient Follow-up Form (case report form page, Form 00), which will be used for purpose of long-term or emergency follow-up, if needed. This will be treated with strict adherence to professional standards of confidentiality and will be filed at Abbott Laboratories under adequate security and restricted accessibility.

The Confidential Patient Follow-up Form should be completed prior to entry of the patient into the study. In addition to the address of the investigator and investigative site, the home address, phone number, social security number, and birth date of the patient should be recorded. The name, address, and phone number of another person who can be contacted in an emergency should also be recorded as well as that person's relationship to the patient.

All other case report forms will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the patient's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the case report forms.

6.0 Investigator and Study Administrative Structure

6.1 Investigative Site

A single investigative site will perform the study and receive study drug supplies. The principal investigator for the study will be:

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

15

Stephen E. Daniels, D.O.
SCIREX Corporation
1305 Wonder World Drive, Suite #202
San Marcos, TX 78666
Telephone: (512) 754-6911

6.2 Sponsor Information

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this single-center study. Abbott Laboratories will manage the administration of the study. The protocol and case report forms (CRFs) will be developed by Abbott Laboratories.

Abbott Laboratories will qualify and select the investigational site and investigator. Abbott representatives will conduct the prestudy site visit, site monitoring, and poststudy visit as well as the management of the study drug supplies. Abbott monitors will prepare the trip reports for each monitoring visit performed, detailing the activities conducted at the visit with any relevant observations.

The database for this study will be created using NOMAD[®], a validated data management system. Designated statisticians at Abbott Laboratories will be responsible for the statistical analysis of the data.

6.3 Clinical Supply Management

Clinical supplies will be prepared by Abbott Laboratories and sent to the site. Abbott Laboratories will authorize release of the clinical supplies once the appropriate essential documents are received. The site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records, and records for return of used and unused clinical supplies to Abbott Laboratories.

6.4 Central Laboratories

Laboratory assessments for hematology including PT and PTT, blood chemistry, and urinalysis, serum cotinine, and hepatitis and urine drug screening will be performed by one central laboratory. The central laboratory for this study is:

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

16

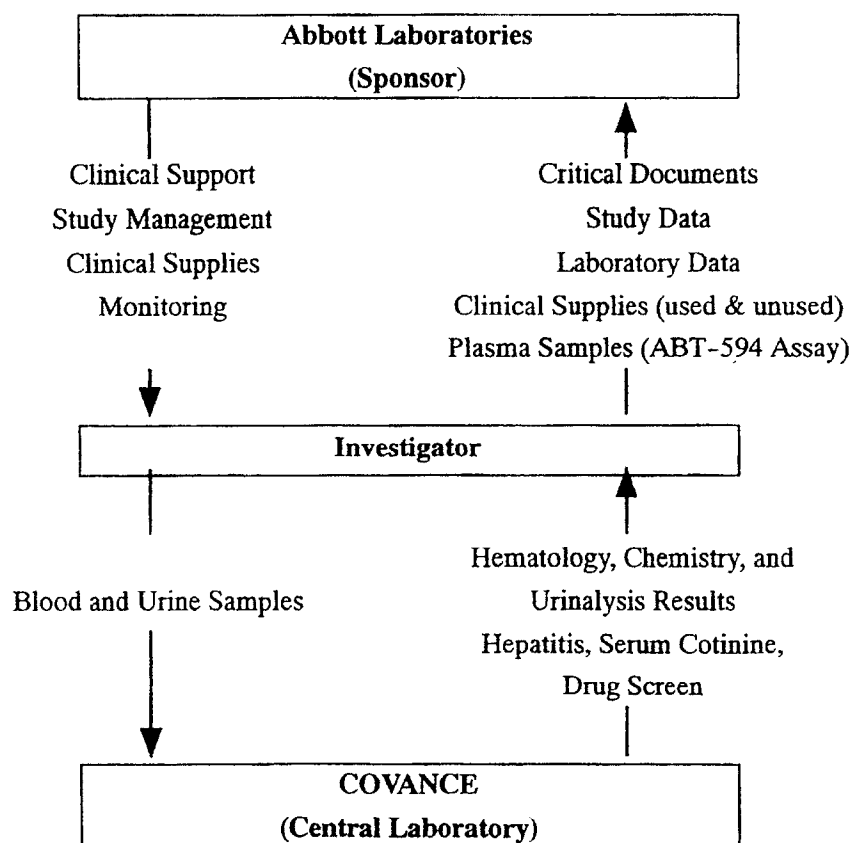
COVANCE
 8211 SciCor Drive
 Indianapolis, IN 46214
 Telephone: (800) 462-8887

All ethanol breath tests and urine pregnancy tests will be performed by designated staff at the investigative site. All ABT-594 plasma assays will be performed by the Drug Analysis Department of Abbott Laboratories, Abbott Park, Illinois.

6.5 Administrative Structure

The administrative structure for this study is depicted in Figure 6.5A.

Figure 6.5A: Administrative Structure



**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

17

7.0 Introduction

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. In the United States, millions of operations are performed annually, most involving some form of acute pain management. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹ For patients with cancer, it has been estimated that pain is experienced by 20% to 50% of patients at the time of their diagnosis, with up to 75% of those with advanced cancer experiencing pain.²

Currently, there are three major groups of therapeutics for pain relief: 1) acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs); 2) opioids, and 3) adjuvant compounds (e.g., antidepressants, sedative-hypnotics). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with acetaminophen and NSAIDs range from gastrointestinal bleeding for NSAIDs, to hepatic toxicity for acetaminophen. Opioids are used for moderate to severe pain and include such analgesics as morphine. Clinically significant physical dependence and tolerance to analgesia can occur in patients receiving opioids regularly for 7 days or longer, with constipation being a major side effect. Adjuvant compounds are commonly used in combination with analgesics for neuropathic pain and include corticosteroids, psychostimulants, anticonvulsants, and tricyclic antidepressants (TCAs). Unlike the other two groups, the majority of adjuvant compounds require slow titration (weeks) which delays the onset of analgesia. Therefore, a class of compounds with the broad spectrum clinical activity and without the liabilities of opioids would represent an important advance in therapeutics for pain relief.

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has recently been enhanced by the discovery that (\pm)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.³ The antinociceptive effects of (\pm)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (\pm)-epibatidine appears to be a potent antinociceptive agent that

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

18

acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (\pm)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.⁴ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is novel neuronal nAChR ligand that is 30- to 100-fold more potent than morphine. ABT-594 demonstrates comparable analgesic activity to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

19

To date, two Phase I clinical studies of ABT-594 have been conducted. Approximately 117 human volunteer subjects have received at least one dose of ABT-594 ranging from 25 µg to 200 µg either after a 10-hour fast (fasted conditions) or approximately thirty minutes after a meal (fed conditions). An unpreserved oral liquid formulation of ABT-594 was used for these studies.

In the single rising dose study (M97-676), 53 subjects received single doses of an oral liquid formulation of ABT-594 ranging from 30 µg to 200 µg under fasted or fed conditions in eight dosing groups. Twenty-four placebo subjects were also involved in the study. In each dose group, up to seven subjects received ABT-594 and three subjects received placebo. Thirty-five normal healthy males received either 30 µg, 50 µg, 80 µg, 100 µg, or 150 µg of ABT-594 under fasted conditions. Thirteen normal healthy males received either 150 µg or 200 µg of ABT-594 under fed conditions. Five surgically-sterilized females received 80 µg of ABT-594 under fed conditions.

Significant cholinergic events were observed in four of seven subjects in the 150 µg fasted dose group, one of seven subjects in the 100 µg fasted dose group, and two of seven subjects in the 200 µg fed dose group. ABT-594 was generally well-tolerated at doses up to 100 µg in subjects who were fasted and at 150 µg in subjects who were fed prior to dosing. Most adverse events occurred at ABT-594 doses of 100 µg or greater. The most frequently noted adverse events were dizziness, nausea, headache, vomiting, pallor, somnolence, sweating, diarrhea, paresthesia, vasodilation, and vertigo. Preliminary analysis suggests that ABT-594 shows relatively linear pharmacokinetics at doses up to 150 µg under fasted conditions and that approximately 50% of ABT-594 is excreted unchanged in the urine. No effect of gender or feeding condition was evident on pharmacokinetic parameters.

In Study M97-743, a double-blind, placebo-controlled multiple rising dose study, 82 normal healthy male subjects in seven dosing groups have received a single fixed daily dose of either placebo or ABT-594 (25 µg to 150 µg) for up to 14 consecutive days under fasted or fed conditions. An additional 12 subjects in a twice daily dosing group (Group 8) received two single fixed daily doses, twelve hours apart, of either placebo or

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

20

ABT-594 (75 µg) for up to 14 consecutive days under fed conditions. Within each dose group, up to twelve subjects were randomly assigned in a 2:1 ratio to receive either ABT-594 (n=8) or placebo (n=4).

The study blind has not yet been broken, so preliminary safety results are presented for all subjects, whether in the placebo or active group, unless otherwise specified. One subject who received a single dose of 75 µg of ABT-594 had a presyncopal episode with pallor, bradycardia, hypotension, and telemetry findings of a 15 second third degree heartblock upon orthostasis, thought to be of possible vasovagal etiology. Initial emesis occurred in four subjects after one dose of blinded study drug in the 100 µg fasted dose group, but increased tolerability was noted in the 100 µg, 125 µg and 150 µg dose groups under fed conditions. In Group 8, one subject with baseline T-wave abnormalities on ECG had asymptomatic T-wave inversions after one dose of blinded study drug. The most frequent events noted during fourteen consecutive days of dosing in preliminary unmonitored reports include headache, lightheadedness/dizziness, nausea, vomiting, sensation of warmth or cold, unpleasant taste, postdosing oral sensation, drowsiness, fatigue, sleep disturbance, decreased concentration or coordination, dry mouth, loose stools, stomach pain or epigastric irritation, heartburn, regurgitation (reflux), decreased appetite, cold/rhinitis, back or arm pain, transaminase elevation, sore throat, cough, sneezing, acne, rubor, retching, belching, sweating, paresthesia, chest pain, cannula site irritation or pain, sensation of pressure in the head, borborygmi, flatulence, palpitations, orthostatic hypotension, and conjunctival injection.

8.0 Study Objective

The objective of this study is to assess the safety and efficacy of single dose administration of four different doses of an oral solution of ABT-594 as compared to ibuprofen 400 mg and placebo, and to evaluate the pharmacokinetics of ABT-594 in patients after third molar extraction surgery.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

21

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This is a Phase II, randomized, parallel group, double-blind, placebo-controlled study to be conducted at a single investigative site in the United States. It is anticipated that approximately 288 patients will be enrolled over the estimated four-month study period. Adult patients between the ages of 18 and 55, inclusive, with at least moderate pain severity within six hours following surgical extraction of two or more impacted third molar teeth and meeting all other selection criteria will be eligible for study participation. Approximately 288 patients will be randomly assigned in equal numbers to six treatment groups with approximately 48 patients per group. Patients will receive a single dose of either one of four different doses of ABT-594, ibuprofen 400 mg, or placebo. Each treatment group will be stratified by patient nicotine use in a 2:1 ratio of non-users (n=32) to users (n=16) of nicotine products.

The study will consist of a Screening Visit in the fourteen days prior to surgery, a Study Confinement Period consisting of third molar extraction surgery, study drug administration, and subsequent study assessments, and a Follow-up Visit five to nine days after study drug administration.

At the Screening Visit within the two weeks before surgery, patients will be evaluated via medical history (including nicotine product use) and physical examination with vital signs, laboratory hematology (including PT and PTT), chemistry, and urinalysis assessment, 12-lead electrocardiogram (ECG), serum cotinine level and screening for hepatitis, drugs of abuse, and, if female, pregnancy. After screening, patients will be categorized as nicotine users (i.e., regular, daily use of nicotine products) or non-users (i.e., no nicotine product use for at least six months prior to third molar extraction surgery) based on patient history of nicotine product use and verified by serum cotinine level.

The Study Confinement Period begins on the day of surgery. Upon arrival at the investigative site for scheduled surgery, patients will undergo an interim assessment of nicotine product use, baseline hematology (including PT and PTT), chemistry, and

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

22

urinalysis testing, a breath test for ethanol, and a repeat screen for drugs of abuse and, if female, pregnancy. Patients will then undergo surgical extraction of at least two third molar teeth using lidocaine, with or without epinephrine, as a local anesthetic.

Following surgery, patients will be instructed to notify the study coordinator when the post-surgical pain level reaches at least moderate severity (as determined by the four-point Pain Intensity Categorical Scale). Patients whose pain intensity does not reach at least moderate severity by six hours after surgery will not be enrolled in the study. Patients with at least moderate pain severity within six hours following surgical extraction of two or more impacted third molar teeth and meeting all other selection criteria will be eligible for study participation.

Baseline (0 hour) pain intensity will be assessed within five minutes prior to study drug administration via the four-point Pain Intensity Categorical Scale and the Pain Intensity Visual Analog Scale (VAS). Additional assessments of pain intensity and pain relief via the four-point Pain Intensity Categorical Scale, the Pain Intensity Visual Analog Scale and the five-point Pain Relief Categorical Scale will be performed at 0.25 (15 minutes), 0.50 (30 minutes), 0.75 (45 minutes), 1, 1.5, 2, 3, 4, 5, 6, 12, and 24 hours after study drug administration. Additionally, the time to first noticeable pain relief (i.e., onset of pain relief) and the time to first meaningful pain relief (i.e., 50% reduction in pain from baseline) will be determined via the stopwatch methodology. A patient global evaluation of analgesic relief due to study drug will also occur at six hours post-study drug administration. While the use of analgesic rescue medication is allowable at any time during the study, patients will be encouraged to delay the use of analgesic rescue medication for at least 90 minutes after study drug administration. Ice packs will be removed approximately 15 minutes prior to pain assessments.

Approximately one-half of all patients (96 nicotine non-users, 48 nicotine users) will also be assigned to have blood samples collected at specified intervals (as per Section 9.5.3) for pharmacokinetic analysis. All patients will be confined at the site for a minimum of 24 hours after study drug administration, regardless of whether analgesic

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

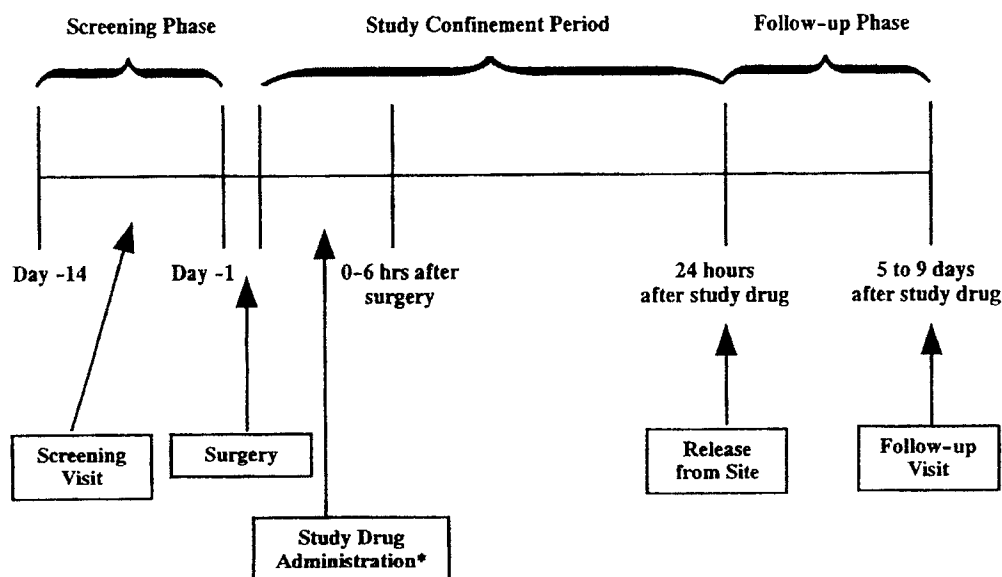
ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

23

rescue medication is utilized. At the end of this period, all patients will undergo physical examination with vital signs, laboratory hematology (including PT and PTT), chemistry, and urinalysis testing, and ECG assessment prior to discharge from the study site.

At the Follow-up Visit (five to nine days after study drug administration), patients will undergo physical examination with vital signs, assessment of adverse event occurrence and recent medication use, and follow-up evaluation of any clinically significant laboratory or ECG findings. The study design is depicted in Figure 9.1A.

Figure 9.1A: Study Design



*only patients with post-surgical dental pain of at least moderate severity

Over the anticipated four-month course of the study, dosing will occur in two separate segments. Each segment will contain 144 patients. In each segment, 24 patients will be randomized to placebo, 24 patients will be randomized to ibuprofen 400 mg, 48 patients will be randomized to a lower dose of ABT-594, and 48 patients will be randomized to a higher dose of ABT-594. In each segment, there will be a 2:1 ratio of nicotine non-users (NIC-) to nicotine users (NIC+) within each treatment group as specified in Table 9.1A.

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two – June 22, 1998

24

Table 9.1A: Dosing Segments					
Segment I			Segment II		
# of Patients		Study Drug Assignment	# of Patients		Study Drug Assignment
NIC-	NIC+		NIC-	NIC+	
32	16	ABT-594 25 µg*	32	16	ABT-594 50 µg*
32	16	ABT-594 75 µg**	32	16	ABT-594 100 µg**
16	8	Ibuprofen 400 mg	16	8	Ibuprofen 400 mg
16	8	Placebo	16	8	Placebo

*Low ABT-594 dose, **High ABT-594 dose

After the first dosing segment is completed, a blinded safety assessment will be performed prior to proceeding to the next segment. After review of blinded safety findings and discussion between the study sponsor and the investigative site, doses of ABT-594 may be adjusted from those specified in Table 9.1A for the next segment. Doses of ABT-594 will not exceed 100 µg. This segmental design affords the flexibility of better defining the dose-response curve while simultaneously optimizing definition of the upper limits of tolerability in patients in an acute pain state as discussed in Section 9.2.

9.2 Discussion of Study Design

The design of this study provides a placebo control group to assess effectiveness of ABT-594 and an active control group to assess results of this study in the context of other published dental pain research. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences.

The four ABT-594 dose groups in this study will be dosed in two separate segments:

Segment I: 25 µg of ABT-594, 75 µg of ABT-594, placebo, ibuprofen

Segment II: 50 µg of ABT-594, 100 µg of ABT-594, placebo, ibuprofen

Safety will be reviewed in a blinded manner between segments. This segmental design provides an opportunity to review safety findings before proceeding to the next higher dose of ABT-594. If the next higher dose is not advisable, this affords the opportunity for incremental dose adjustment between segments in order to better define a dose-response curve and the limits of tolerability.

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 3

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

25

Flexibility of dosing is obtained at the risk of significant differences in response between the two segments. The inclusion of placebo and ibuprofen in each segment will allow an assessment of the magnitude of any segment differences and permit statistical adjustments if needed. Overlapping ABT-594 doses across segments will provide robustness in fitting dose-response curves because curves can be fitted with and without a single dose segment across a large dose range.

9.3 Selection of Study Population

It is anticipated that 288 patients will be randomized and receive study drug in this study. Adult patients between the ages of 18 and 55, inclusive, with at least moderate pain severity within six hours following surgical extraction of two or more impacted third molar teeth requiring bone removal are eligible for enrollment in this study provided that they meet all of the inclusion criteria outlined in Section 9.3.1 and do not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

1. Prior to any study specific procedure, voluntary written informed consent must be obtained from each patient after the purpose and nature of the study have been explained.
2. Patients will be males and females between the ages of 18 and 55 years, inclusive.
3. The patient's weight should be between 45 kg and 120 kg with weight proportional to height as judged by the investigator.
4. Patients will be judged to be in good health, based upon the results of medical history, physical examination with vital signs, and laboratory profile.
5. Patients will have a 12-lead electrocardiogram without clinically significant abnormality.
6. Patients will be ambulatory.
7. Females must be non-lactating and:
 - at no risk of pregnancy for one of the following reasons: postmenopausal for at least one year, hysterectomy, or tubal ligation, or
 - of child-bearing potential with a negative prestudy HCG (beta human chorionic gonadotropin) pregnancy test and be utilizing oral or barrier

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

26

contraceptive methods throughout the study (a partner with a vasectomy is not an acceptable barrier method).

8. Patients will have had surgical extraction of two or more impacted third molar teeth, at least one of which must be mandibular requiring bone removal. If only two third molars have been removed, they must be ipsilateral.
9. Patients will have post-surgical dental pain of at least moderate severity (i.e., as determined by the four-point Pain Intensity Categorical Scale located in Appendix C) within six hours of third molar extraction surgery.

9.3.2 Exclusion Criteria

1. Patients who acknowledge having taken any drug, including over-the-counter medication, within 12 hours prior to third molar extraction surgery (except for females taking oral contraceptives or hormone replacement therapy) as specified in Section 9.4.7. For long-acting or sustained-release formulations, a longer interval may be necessary as determined by the investigator.
2. Patients who are unwilling to abstain from taking any medications or tobacco or other nicotine products (e.g. chew, gum, or patches) for 24 hours after receiving study drug (except for females taking oral contraceptives or hormone replacement therapy, the allowable analgesic rescue medications, and those medications deemed medically necessary for the well-being of the patient by the investigator as specified in Section 9.4.7).
3. Patients with a known history of or positive tests for hepatitis or HIV.
4. Patients with a history of alcoholism or drug addiction within 12 months prior to third molar extraction surgery including patients with positive test results for drugs of abuse or ethanol use.
5. Patients with a relevant history of drug sensitivity or drug allergy or contraindication to use of ibuprofen, nicotinic agonists, analgesic rescue medications or other medications utilized in this study.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594

Protocol M97-772

Incorporating Amendments One and Two - June 22, 1998

27

6. Patients with a history or presence of seizure (including childhood febrile seizures), diabetes, cancer, active peptic ulcer disease, coagulopathy or any clinically significant cardiac, respiratory, metabolic, renal, hepatic, gastrointestinal, dermatologic, venereal, hematologic, neurologic, or psychiatric disease or disorder in the investigator's opinion.
7. Patients who have had any clinically significant illness/infection or who have had any surgical procedure, other than the present third molar extraction surgery, within one month prior to screening.
8. Patients who have open wounds or buccal, gingival, or sublingual ulcers or visible oral lesions prior to third molar extraction surgery.
9. Patients who have received an investigational drug within one month prior to administration of study drug or who are scheduled to receive an investigational drug other than ABT-594 during the course of this study.
10. Patients who have donated blood within one month prior to study drug administration.
11. Patients with diastolic blood pressure greater than 100 mm Hg and/or systolic blood pressure greater than 180 mm Hg (sitting).
12. Patients who have visual, hearing, or communication disabilities that, in the investigator's opinion, impair the ability to participate in the trial.
13. Patients who, in the opinion of the investigator, are unlikely to comply with the study protocol or who are unsuitable for any other reason.
14. Patients who have received general anesthesia or benzodiazepine administration during third molar extraction surgery. Only local anesthesia (including nerve block) with or without vasoconstriction is permissible during third molar extraction surgery.
15. Patients who do not meet protocol-defined criteria for a nicotine user or nicotine non-user, as specified in Section 9.5.1.2.
16. Patients who have a history or current presence of nasal polyps, bronchospasm, or angioedema induced by NSAIDs.
17. Patients who have a clinically significant abnormality in clinical chemistry, hematology, or urinalysis, including AST or ALT > 1.5 upper limit of the reference range or calculated creatinine clearance (CrCl) < 80 mL/min at screening.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

28

18. Patients who have been previously participated in a study involving ABT-594 including the present study.

9.3.3 Removal of Patients from Therapy or Assessment

A patient may voluntarily discontinue participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to prematurely terminate a patient. If a patient is terminated from the study, the investigator must notify the Abbott monitor within 24 hours and document the reason for termination on the appropriate case report form.

If a patient is prematurely terminated or receives analgesic rescue medication within 24 hours of study drug administration, then pain assessments via the four-point Pain Intensity Categorical Scale, the Pain Intensity VAS, and the five-point Pain Relief Categorical Scale should be performed at the time of termination or prior to receiving rescue medication. For those patients who prematurely terminate or receive analgesic rescue medication within six hours of study drug administration, the patient global evaluation of analgesic relief due to study drug should also be performed at the time of termination or prior to receiving rescue medication. Patients should be confined at the site for a minimum of 24 hours after study drug administration.

In the event that a patient is prematurely terminated from the study, the following procedures should be performed prior to release of the patient from the investigative site: physical examination with vital sign determination, laboratory hematology (including PT and PTT), chemistry, and urinalysis testing, ECG assessment, and pharmacokinetic sampling, if applicable. All patients with clinically significant abnormalities in laboratory values will be followed until the normalization or stabilization of the laboratory value or a satisfactory explanation for the abnormality is determined and clinical judgment dictates further laboratory assessments are unwarranted.

If a patient's acute medical condition prior to study drug administration on Day 1 (i.e. the day of third molar extraction surgery) changes from the Screening Visit such that the patient no longer meets study selection criteria on Day 1, the patient will not be eligible for study participation.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

29

If, in the judgment of the investigator or Abbott Laboratories, continued exposure to a study drug represents a significant risk to patients, the study will be terminated.

9.4 Treatments

A reconstituted oral solution of ABT-594 will be utilized in this study.

The placebo oral solution to be used in this study will be Sterile Water for Injection, United States Pharmacopeia (USP).

Encapsulated ibuprofen 200 mg tablets and matching placebo capsules will also be used.

In this study, patients will be randomized to one of the following six treatment groups, as described in Table 9.4A:

1. 25 µg of ABT-594 oral solution
2. 50 µg of ABT-594 oral solution
3. 75 µg of ABT-594 oral solution
4. 100 µg of ABT-594 oral solution
5. Ibuprofen 400 mg
6. Placebo

9.4.1 Treatments Administered

Patients will be assigned in equal numbers to one of six treatment groups as specified in Table 9.4A. Each patient will receive a 10.0 mL liquid dose (either ABT-594 oral solution, ABT-594 oral solution plus placebo oral solution, or placebo oral solution) and two capsules (either ibuprofen or placebo).

The pharmacist and an assistant to the pharmacist at the investigative site will be unblinded to the study randomization and will prepare study drug using specific instructions provided by Abbott Laboratories. The site pharmacist will prepare the liquid and capsules for administration as described in Section 9.4.2.2. The assistant to the pharmacist will be present during the study drug preparation in order to verify the oral solution preparation and dispensing procedures. The pharmacist and the assistant will

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

30

not be involved in any other aspect of the study. Other designated clinical personnel at the investigative site, who are blinded to study drug assignment, will administer the study drug to the patient.

The liquid dose of study drug will be administered directly into the patient's mouth using an oral syringe prefilled with the final patient dose, as specified by the randomization schedule. After administration of the 10 mL of oral liquid, two capsules will then be administered to be followed by the ingestion of at least 250 mL of water. The time of study drug administration will be recorded to the nearest minute. No foods or nutrient liquids, other than water, will be allowed for two hours following study drug administration. Two hours after study drug administration, patients will receive a standardized soft diet; water will be allowed *ad libitum* during the remainder of the study.

In order to minimize the effects of posture upon absorption, it is recommended that patients should avoid the supine position for a minimum of two hours following study drug administration.

Table 9.4A summarizes the study drug administration for each treatment group. The study drug will be administered under fasted conditions (i.e., after at least a 6- to 10-hour fast).

Table 9.4A: Study Drug Administration					
Treatment Group	Number of Patients	Volume of ABT-594 Oral Solution	Volume of Placebo Oral Solution	Number of Ibuprofen 200 mg Capsules	Number of Placebo Capsules
ABT-594 25 µg	48	2.5 mL	7.5 mL	0	2
ABT-594 50 µg	48	5.0 mL	5.0 mL	0	2
ABT-594 75 µg	48	7.5 mL	2.5 mL	0	2
ABT-594 100 µg	48	10.0 mL	0	0	2
Ibuprofen 400 mg	48	0	10.0 mL	2	0
Placebo	48	0	10.0 mL	0	2

An oral syringe will be used to draw up the 10 mL final dose to be administered to the patient.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

31

9.4.2 Identity of Investigational Products

Oral Solution (Liquid): ABT-594 powder for oral solution will be packaged in bottles. Each bottle will contain 50.5 mg ABT-594 Base Equivalents. The oral solution will be prepared by reconstituting the ABT-594 powder for oral solution with Sterile Water for Injection, USP, to provide a final 10 µg/ml base equivalent solution. Preparation directions for reconstitution and serial dilution of the powder to make the final 10 ml dose will be provided by Abbott Laboratories to the investigative site pharmacist. The ABT-594 oral solution and placebo for oral solution to match ABT-594 oral solution will be liquid formulations identical in appearance.

Capsules: The ibuprofen and matching placebo will be capsules identical in appearance and packaged in plastic bottles. The ibuprofen 200 mg tablets will be encapsulated in an Iron Gray Opaque No. 00 size capsule (identical to the placebo capsule) in order to keep the study drug appropriately blinded. Capsules will be provided in bulk bottles.

Table 9.4B displays the test preparations with the drug product lot numbers.

Table 9.4B: Identification of Test Preparations	
Test Preparation	Drug Product Lot Numbers
ABT-594 Powder for Oral Solution, 50.5 mg (Base Equivalents) per Bottle	40-921-AR-01
Sterile Water for Injection, USP, to be utilized as a placebo to match ABT-594 oral solution and for reconstitution of ABT-594 Powder for Oral Solution	To Be Determined
Ibuprofen 200 mg capsules	31-782-AR-03
Placebo capsules to match ibuprofen capsules	86-591-AR

9.4.2.1 Packaging and Labeling

The ABT-594 powder for oral solution and placebo oral solution to match ABT-594 oral solution will be supplied and packaged by Abbott Laboratories Investigational Drug Services (D-492), North Chicago, Illinois. The ABT-594 powder for oral solution will be packaged in bottles. Each bottle will contain 50.5 mg ABT-594 Base Equivalents. Each bottle will bear a single panel, computer-generated label that will include the

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

32

following information: study number, contents of bottle, storage requirements, packaging lot number, instructions for use, and Abbott address. ABT-594 powder for oral solution should be kept at controlled room temperature between 68-77°F (20-25°C). Storage conditions for the reconstituted oral solution will be included with the detailed instructions for study drug preparation supplied to the site pharmacist by Abbott Laboratories.

Sterile Water for Injection should be stored at labeled conditions.

The ibuprofen and matching placebo capsules will be supplied and packaged by Abbott Laboratories Investigational Drug Services (D-492), North Chicago, Illinois. The capsules will be supplied in bulk bottles and will be stored at labeled conditions.

The liquid and capsules will be supplied in separate bulk bottles. Each bottle will be individually labeled to identify the dosage formulation (liquid or capsule), the New Product Research Order (NPRO) number and packaging lot number, quantity of contents, dosage strength, active or placebo ingredients (ABT-594, ibuprofen, or placebo), and instructions for storage.

All materials required for preparation of the oral liquid doses, as specified in the detailed dispensing procedures, will be supplied by Abbott Laboratories to the investigative site.

9.4.2.2 Study Medication Preparation

The pharmacist will prepare the study drug according to Table 9.4A. Specific directions will be provided to the pharmacist by Abbott Laboratories and will be included with the randomization schedule.

The site pharmacist will reconstitute the ABT-594 powder for oral solution daily and prepare the specified dose for each patient throughout the day on an "as needed" basis at the study site. An assistant to the pharmacist will be present during study drug preparation in order to verify the oral solution preparation and dispensing procedures.

The pharmacist will also select which type of capsules (placebo or ibuprofen) are to be administered to the patient using the randomization schedule. The pharmacist will not be involved in any other aspect of the study.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

33

The study-designated pharmacist at the investigative site will ensure that the randomization schedule is secured, so that no other study personnel become unblinded.

9.4.2.3 Storage and Disposition of Supplies

ABT-594 powder for oral solution, placebo oral solution, ibuprofen capsules, and matching placebo must be stored at labeled conditions. All clinical supplies must be stored in an appropriate secure place until use or return to Abbott Laboratories.

Detailed study medication preparation records will be maintained by the pharmacist.

The investigator agrees not to supply study drug to any persons except to those patients enrolled in the study or to those named as sub-investigators. The investigator will keep a current and accurate inventory of all clinical supplies received from Abbott Laboratories and dispensed to the patients. Upon termination of the study, all used and unused original drug containers and remaining materials supplied by Abbott Laboratories will be returned for destruction, following instructions from the clinical monitor.

9.4.3 Method of Assigning Patients to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by the Department of Clinical Statistics at Abbott Laboratories. The patients will be randomized in equal numbers (48 patients per treatment group) to receive ABT-594 25 µg, ABT-594 50 µg, ABT-594 75 µg, ABT-594 100 µg, ibuprofen 400 mg, or placebo. For each dosing segment, separate randomization schedules will be generated for nicotine non-users and nicotine users (as determined at screening). In each segment there will be a 2:1 ratio of nicotine non-users (NIC-) to nicotine users (NIC+) within each treatment group. Each segment will contain 24 patients randomized to placebo (16 NIC-, 8 NIC+ patients), 24 patients randomized to ibuprofen 400 mg (16 NIC-, 8 NIC+ patients), 48 patients randomized to a lower dose of ABT-594 (32 NIC-, 16 NIC+ patients), and 48 patients will be randomized to a higher dose of ABT-594 (32 NIC-, 16 NIC+ patients) as specified in Table 9.1A. All patients will be assigned identification numbers in numerical sequence as they experience post-surgical pain of at least moderate severity. In order to equitably distribute baseline severity across treatment groups,

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

34

patients experiencing moderate post-surgical pain will be assigned identification numbers in ascending numerical sequence, while the patients experiencing severe post-surgical pain will be assigned identification numbers in descending numerical sequence. Patients will be given study drug based on their identification numbers.

9.4.4 Selection of Doses in the Study

In the Phase I single rising dose study (M97-676), 53 subjects, 48 normal healthy males and 5 surgically-sterilized females, received single doses of an unpreserved oral liquid formulation of ABT-594 ranging from 30 µg to 200 µg under fasted or fed conditions. Significant cholinergic events were observed in four of seven subjects in the 150 µg fasted dose group, one of seven subjects in the 100 µg fasted dose group, and two of seven subjects in the 200 µg fed dose group. ABT-594 was generally well-tolerated at doses up to 100 µg in subjects who were fasted and at 150 µg in subjects who were fed prior to dosing. Most adverse events occurred at ABT-594 doses of 100 µg or greater. Based on the findings of the single rising dose study, the range of ABT-594 doses was selected for this study. In terms of efficacy, no human data exists regarding the dose range of analgesic efficacy for ABT-594. The 400 mg ibuprofen dose was selected since it has been used as a standard comparator dose in clinical trials of other analgesic agents.

9.4.5 Selection and Timing of Dose for Each Patient

Approximately 288 patients will be randomly assigned in equal numbers to one of six treatment groups with approximately 48 patients per group. Patients will receive a single dose of either 25 µg, 50 µg, 75 µg, or 100 µg of an ABT-594 oral solution, ibuprofen 400 mg, or placebo after third molar extraction surgery. Randomization will occur and study drug will be administered only after patients report post-surgical dental pain of at least moderate severity (as determined by the four-point Pain Intensity Categorical Scale). Patients whose pain does not reach at least moderate severity within six hours following third molar extraction surgery will not be randomized nor receive study drug.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

35

9.4.6 Blinding

The designated pharmacist at the investigative site will prepare the study drug according to the randomization schedule provided by Abbott Laboratories. Only the pharmacist and the assistant will be unblinded to the study drug assignments and will not be involved in any other part of the clinical trial. The assistant will be present during the daily reconstitution of the powder for oral solution and the study drug preparation for each patient in order to verify the amount of solution being dispensed. All other study personnel, including the principal investigator, as well as the patients will remain blinded to the patient's treatment throughout the course of the study. The study-designated pharmacist at the investigative site will ensure that the randomization schedule is secured, so that no other study personnel become unblinded.

The randomization schedule, determining patient treatment by patient number, will be computer-generated by Abbott Laboratories Department of Clinical Statistics prior to study start. All enrolled patients will be randomized in equal numbers to one of six treatment groups discussed in Section 9.4.1 (Tables 9.1A and 9.4A). All patients will be assigned identification numbers in numerical sequence, as described in Section 9.4.3, at the timepoint when post-surgical dental pain of at least moderate severity is reported following third molar extraction surgery. All patients will receive 10 mL of liquid and two capsules for purposes of blinding.

A document which contains the study drug assignment for each patient will be provided to the investigator in a separate sealed envelope. The study blind envelope may be broken if, in the opinion of the investigator, it is in the patient's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) must be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. The sponsor must then be notified within 48 hours of the blind being broken. The date, time, and reason that the blind was broken must be recorded on the appropriate case report form.

Once the study is complete, the sealed envelopes will be sent to Abbott Laboratories as part of the case report form.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

36

9.4.7 Prior and Concomitant Medication

No medications, including over-the-counter medications, will be allowed from 12 hours prior to third molar extraction surgery until 24 hours following study drug administration, other than the use of approved analgesic rescue agents or antiemetics, or other medications deemed medically necessary by the study investigator. The use of oral contraceptives and hormone replacement therapy will be allowed for female patients, but must be taken at least two hours before or after the study drug is administered.

Routine postoperative concomitant medications will be restricted to analgesic rescue medications and antiemetics. No prophylactic antiemetic therapy will be allowed during the course of the study. If an antiemetic is used, dopamine antagonists (including phenothiazines) should be avoided. Ondansetron hydrochloride (Zofran®) is the preferred antiemetic agent. Analgesic rescue medications that may be used include acetaminophen (1000 mg, orally), hydrocodone bitartrate 5 mg and acetaminophen 500 mg (Lortab® 5/500, orally), hydrocodone bitartrate 7.5 mg and acetaminophen 500 mg (Lortab® 7.5/500, orally), and meperidine (Demerol®, 50 mg intramuscularly).

Any medications taken by the patient within the four weeks prior to study randomization, particularly any analgesic medications, should be recorded on the appropriate case report form.

All patients must be able to abstain from use of tobacco or other nicotine products for 24 hours after study drug administration.

9.4.8 Treatment Compliance

Designated site personnel, who are blinded to study drug assignment, will administer the study drug to each patient to ensure compliance.

9.4.9 Drug Accountability

Study drug shipped to the site will be verified by the investigator or designee regarding the amount shipped and that all the supplies were received intact. This will be documented by signing and dating the shipping account memorandum (SAM) or similar

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

37

document. Study drug will be dispensed in ascending or descending numerical sequential order, depending on post-surgical pain severity (as described in Section 9.4.3), to each patient who meets the enrollment criteria by the investigator according to the patient numbers provided to the site. The investigator or designee will record the patient number, patient initials and date dispensed.

The investigative site pharmacist must keep an accurate running inventory of study drug to include the lot number and SAM number(s), the total amount of liquid dispensed, the number of capsules dispensed, and the date the study drug was dispensed for each patient. Upon completion of the study, the original containers (including all bottles, syringes, and labels), whether empty or containing unused study drug, will be returned to Abbott Laboratories for destruction following the instruction from the Abbott monitor. All used and unused study drug must be inventoried on the form provided by Abbott Laboratories (see Attachment I).

An overall accountability of the study drug will be performed and verified by the Abbott monitor or designee throughout the study and at the site close-out visit.

9.5 Efficacy, Pharmacokinetic, and Safety Variables

9.5.1 Efficacy, Pharmacokinetic, and Safety Measurements to be Assessed and Flow Chart

Study procedures will be performed as summarized in Table 9.5A, Study Flow Chart.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

38

Table 9.5A: Study Flow Chart

Study Procedures	Screening Visit	Study Confinement Period												Follow-up Visit		
		Surgery	0 Hr	(hours after dosing)												
				0.25	0.50	0.75	1	1.5	2	3	4	5	6	12	24	5-9 days
Informed Consent	•															
Medical History	•	• ^l														
Physical Examination	•															
Vital Signs	•		• ^a					•		•			•		• ^h	•
12-lead Electrocardiogram	•														• ^h	• ^g
Laboratory Assessments ^b	•	• ^c													• ^h	• ^g
Creatinine Clearance Calculated	•														• ^h	• ^g
Hepatitis A, B, C	•															
Urine Drug Screen	•	• ^c														
Serum Cotinine	•															
Ethanol Breath Screen		• ^c														
Female Pregnancy Test	•	• ^c														
Third Molar Extraction		•														
Study Drug Administration			• ^d													
Pain Assessments (Appendix C)			• ^{a,e}	•	•	•	•	•	•	•	•	•	•	•	• ^k	
Adverse Event Monitoring		• ^c	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant Medication Assessment	•	• ^c	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Pharmacokinetic Sampling ^j			• ^a												•	•
Patient Global Evaluation															• ^f	
^{a.} Immediately prior to dosing. ^{b.} Hematology (including PT & PTT), clinical chemistry, urinalysis. ^{c.} Performed upon arrival at the site. ^{d.} Once patient experiences post-surgical pain of at least moderate severity. ^{e.} Four-point Pain Intensity Categorical Scale and VAS only. ^{f.} A Patient Global Evaluation will be completed at 6 hours or upon premature termination or immediately prior to receiving rescue medication, if the latter two events occur less than 6 hours post-study drug administration. ^{g.} Performed only if there are clinically significant abnormalities at the previous evaluation. ^{h.} Performed for all patients prior to leaving the site. ^{i.} Only patient use of tobacco or nicotine products in the interval since the Screening Visit will be collected. ^{j.} Performed on the first 48 NIC- patients and the first 24 NIC+ patients of each dosing segment (one-half of all patients). ^{k.} At the last hourly observation or upon premature termination or immediately prior to receiving rescue medication, if the latter two events occur less than 24 hours post-study drug administration.																

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 4

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

39

9.5.1.1 Informed Consent

The investigator or designated representative will explain the nature of the study to the patient, and answer all questions regarding this study. Prior to any screening procedures being performed on the patient, the informed consent statement will be reviewed and signed and dated by the patient and the person who administered the informed consent. A copy of the informed consent form will be given to the patient and a copy will be placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the patient received a signed copy.

9.5.1.2 Medical History (including nicotine product use)

A complete medical history, including documentation of nicotine use, will be obtained from each patient during the Screening Visit. Upon arrival at the site prior to surgery on Day 1, patient use of tobacco or nicotine products in the interval since the Screening Visit will be collected.

A patient history of nicotine product use will be obtained at the screening visit and recorded on the appropriate case report form. After screening, patients will be categorized as nicotine users (NIC+) or nicotine non-users (NIC-) based on patient history of nicotine product use (and verified by serum cotinine level). Nicotine users (NIC+) will be individuals with a history of regular use of tobacco or other nicotine products (e.g., chew, gum, patches) on a daily basis for at least one month prior to third molar extraction surgery. Nicotine non-users will be individuals with a history of no use of tobacco or other nicotine products for at least six months prior to third molar extraction surgery. Patients who do not meet criteria for a nicotine user or non-user will be ineligible for study entry.

9.5.1.3 Physical Examination

A physical examination, including weight, will be performed at the Screening Visit, 24 hours after study drug administration, and at the Follow-up Visit. Height will be obtained at the Screening Visit only. The physical examination performed at the Screening Visit will serve as the baseline physical examination.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

40

9.5.1.4 Vital Signs

Blood pressure, pulse rate, respiration rate, and body temperature will be taken at the Screening Visit, immediately prior to study drug administration (0 hour), at 1.5, 3, 6 and 24 hours after receiving study drug, and at the Follow-up Visit.

All protocol-specified blood pressure and heart rate measurements should be obtained after the patient has been sitting for at least three minutes. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Patients should not wear tight sleeves. Ideally, the patient's blood pressure should be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws (predose, 6 and 24 hours after dosing). Mental activity, especially talking, causes the blood pressure to rise, therefore, the patient should not engage in conversation either during or shortly before blood pressures are recorded. Patients should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

9.5.1.5 Electrocardiogram (ECG)

A 12-lead ECG will be obtained at the Screening Visit and at 24 hours after study drug administration. The ECG performed at the Screening Visit will serve as the baseline ECG. A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the Abbott monitor with the case report form (CRF). A 12-lead ECG will be performed at the Follow-up Visit, only if clinically significant changes are present on the previous evaluation.

9.5.1.6 Clinical Laboratory Testing

Samples will be obtained for the laboratory determinations listed in Table 9.5B at the Screening Visit, upon arrival at the site on the day of surgery (Day 1), and at 24 hours after study drug administration. The laboratory determinations on Day 1 will serve as the baseline assessments. Laboratory determinations will be performed at the Follow-up Visit, only if clinically significant changes are present on the previous evaluation.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

41

Table 9.5B: Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
RBC count	Total bilirubin	pH
WBC count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Bilirubin
Neutrophils	Serum glutamic-oxaloacetic transaminase (SGOT/AST)	Protein
Monocytes	Lactic Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Lymphocytes	Chloride	
MCHC/MCV/MCH	Calcium	
Platelet count (estimate not acceptable)	Inorganic phosphorus	
Prothrombin Time (PT)	Uric Acid	
Partial Thromboplastin Time (PTT)	Bicarbonate	
	Cholesterol, including LDL, HDL, and VLDL	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

In addition, a creatinine clearance will be calculated at the Screening Visit according to the following formula:

$$\text{MEN: CrCl (ml/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age in yrs})}{72 \times \text{serum creatinine (mg/dl)}}$$

WOMEN: 0.85 x value calculated for men

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

42

The investigator will review all laboratory values. For each abnormal value, the investigator will assess clinical significance and provide an etiology, if clinically significant. The assessment of etiology will use one of the following categories:

- Concurrent Medication (medication must be specified)
- Concurrent Disease (disease must be specified)
- Sample or laboratory error
- Unknown
- Non-fasting specimen (chemistry only)
- Other (must specify)

A copy of each laboratory report must be included with the case report form.

9.5.1.7 Hepatitis Screen

Patients will be screened for Hepatitis A (HAAb), Hepatitis B (HBS Ag), and Hepatitis C (HCV Ab) serologies at the Screening Visit. The hepatitis test panel will be performed by a central laboratory (COVANCE).

9.5.1.8 Urine Drug Screen and Breath Alcohol Screen

Urine specimens will be tested for drugs of abuse at the Screening Visit and upon arrival at the site prior to surgery on Day 1. Urine drug screens will be performed by a central laboratory (COVANCE). An ethanol breath test will also be performed by designated site personnel upon patient arrival at the site prior to surgery on Day 1.

9.5.1.9 Serum Cotinine

A serum cotinine test will be obtained at the Screening Visit. The serum cotinine test will be performed by a central laboratory (COVANCE).

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

43

9.5.1.10 Pregnancy Test

A urine pregnancy test will be performed by designated study personnel at the Screening Visit and upon arrival at the site prior to surgery on Day 1 on all females of child-bearing potential. A lactating or pregnant female will not be eligible for participation in this study.

9.5.1.11 Adverse Event Monitoring

Adverse events will be continuously monitored throughout the study from the time of study randomization through the Follow-up Visit (five to nine days after study drug administration). Adverse events which are spontaneously reported to the investigative site within 30 days following study drug administration will also be captured. All adverse events, whether in response to a query, observed by site personnel, or spontaneously reported by the patient will be recorded in the CRF. Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event (see Section 9.5.4.2). Any severe or serious adverse events will be reported to one of the Abbott Monitors within 24 hours of discovery.

9.5.1.12 Pharmacokinetic Sampling

Approximately 144 patients (one-half of all study patients: 96 NIC- patients and 48 NIC+ patients) will be assigned to undergo pharmacokinetic sampling. In each dosing segment, the first 48 nicotine non-users (NIC-) and the first 24 nicotine users (NIC+) enrolled will be chosen to undergo blood draws for pharmacokinetic testing. Blood samples for assay for ABT-594 will be collected immediately prior to study drug administration (0 hour), 1, 2, 4, 6, 12 and 24 hours after study drug administration. Blood samples should be obtained after any pain assessment or vital sign determination scheduled for that timepoint have been performed.

Handling, storage and shipping instructions can be found in Section 9.5.3.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

44

9.5.2 Efficacy Procedures

Prior to patient pain evaluation, a trained site observer will instruct all potential candidates on how to record each of the measurements of pain intensity, pain relief, and the patient global evaluation. These assessments include a four-point categorical scale and a visual analog scale (VAS) of pain intensity, a five-point categorical scale of pain relief from baseline, and a patient global evaluation of the analgesic relief due to study drug as delineated in Appendix C. The time to first noticeable pain relief (i.e., onset of pain relief) and the time to first meaningful pain relief (i.e., 50% reduction in pain from baseline) will be determined via the stopwatch methodology (Appendix C). A designated trained study coordinator, who is blinded to study drug assignment, will observe and instruct patients regarding pain assessment procedures and will be present as all patient pain assessments are recorded. Patient pain assessments will be recorded on patient pain assessment worksheets which will be retained at the site as part of the source document. Ice packs will be removed 15 minutes prior to pain assessments.

At the time intervals where pharmacokinetics samples will be obtained, pain assessment will precede phlebotomy for these samples.

For patients who prematurely terminate or receive analgesic rescue medication within 24 hours of study drug administration, pain assessments via the four-point Pain Intensity Categorical Scale, the Pain Intensity VAS, and the five-point Pain Relief Categorical Scale will be performed at the time of termination or prior to receiving rescue medication. For those patients who prematurely terminate or receive analgesic rescue medication within six hours of study drug administration, the patient global evaluation of analgesic relief due to study drug should also be performed at the time of termination or prior to receiving rescue medication.

9.5.2.1 Pain Intensity Categorical Scale and Pain Intensity Visual Analog Scale (VAS)

Following third molar extraction surgery, patients will be asked to record post-surgical pain intensity by marking the VAS and completing the four-point Pain Intensity Categorical Scale, as described in Appendix C. Patients will notify the study coordinator

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

45

when the post-surgical pain level reaches at least moderate severity (as determined by the four-point Pain Intensity Categorical Scale). Patients whose pain intensity does not reach at least moderate severity by six hours after surgery will not be randomized and will not receive study drug.

Patients who have post-surgical dental pain of at least moderate severity within six hours following third molar extraction surgery and meeting all other selection criteria will be eligible for study participation.

Baseline (0 hour) pain intensity will be assessed within five minutes prior to study drug administration via the four-point Pain Intensity Categorical Scale and the Pain Intensity Visual Analog Scale.

Additional assessments of pain intensity will be performed at 0.25 (15 minutes), 0.50 (30 minutes), 0.75 (45 minutes), 1, 1.5, 2, 3, 4, 5, 6, 12 and 24 hours after study drug administration.

9.5.2.2 Pain Relief Categorical Scale and Stop Watch Method

The time to first noticeable pain relief (i.e., onset of pain relief) and the time to first meaningful pain relief (i.e., 50% reduction in pain from baseline) will be determined using the stopwatch method described in Appendix C.

Patients will also assess pain relief via the five-point Pain Relief Categorical Scale as described in Appendix C. Pain relief assessments will occur at the same time intervals as the post-baseline pain intensity determinations [i.e., 0.25 (15 minutes), 0.50 (30 minutes), 0.75 (45 minutes), 1, 1.5, 2, 3, 4, 5, 6, 12 and 24 hours after study drug administration].

9.5.2.3 Patient Global Evaluation

The patient global evaluation of analgesic relief due to study drug will only be performed at 6 hours after study drug administration or upon premature termination or prior to receiving analgesic rescue medication if these latter two events occur less than six hours after study drug administration. The patient global evaluation is described in Appendix C.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

46

9.5.2.4 Analgesic Rescue Medication Use

The study site will supply analgesic rescue medication. Analgesic rescue medications that may be used are:

1. Acetaminophen 1000 mg, orally, is the rescue medication of choice.
2. Hydrocodone bitartrate 5 mg or 7.5 mg and acetaminophen 500 mg (Lortab® 5/500 or Lortab® 7.5/500), orally
3. Meperidine 50 mg, intramuscularly.

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 90 minutes following the administration of study drug. The date and time the rescue medication was given as well as the name and dosage regimen of the rescue medication must be collected on the appropriate case report forms.

Patients receiving rescue medication will have a final pain assessment (as described in Section 9.5.2) performed prior to receiving a rescue medication, but no additional pain assessments after rescue medication is given. Patients receiving rescue medication will remain confined to the site for 24 hours after study drug administration and continue to undergo other scheduled study procedures (i.e. vital sign determinations, pharmacokinetic sampling if applicable) including the 24-hour post study drug physical examination with vital signs, laboratory testing, and ECG assessments. After release from the site, patients will return for a Follow-up Visit five to nine days after study drug administration.

9.5.3 Pharmacokinetic Procedures (Drug Concentration Measurements)

9.5.3.1 Collection and Storage of Blood Samples for ABT-594 Plasma Assay

Blood samples for ABT-594 plasma assay will be collected for one-half of all patients (96 NIC- patients and 48 NIC+ patients) immediately prior to study drug administration (0 hour), 1, 2, 4, 6, 12, and 24 hours after study drug administration. One blood sample (approximately 7 ml) will be collected through a heparin lock into a sodium heparinized evacuated collection tube at each time point.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

47

All blood samples will be immediately stored at 4° C or below. The samples will be separated by centrifugation within one hour after sample collection. At least 3 mL of plasma will be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, patient number, initials, date and time of collection relative to dosing. This information will also be recorded on the appropriate case report form. All labeled plastic vials will be placed in a rack to prevent breakage. **Plasma samples for determination of ABT-594 must be frozen at -10° C or lower within one hour from centrifugation.** All specimens will be kept frozen at -10° C or lower until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories. Instructions for the collection and handling of blood samples are given in Appendix D.

9.5.3.2 Shipment of Plasma Samples

An inventory list of the samples included in the shipment must accompany the shipment. The inventory list will include the shipping date, number of samples in the container, drug identification, Abbott protocol number, study monitor, patient numbers, sample type, sampling times, and missing samples. The frozen samples will be packed in dry ice sufficient to last two days during shipping.

Arrangements will be made with Abbott Laboratories for shipping of the plasma samples to the following Abbott address:

Sample Receipt
Abbott Laboratories
Dept. 4TA, Bldg. AP9
100 Abbott Park Road
Abbott Park, IL 60064-3500
Phone: (847) 937-0889
Fax: (847) 938-9898

On the day of shipping, a copy of the inventory sheet should be faxed to the Sample Receiving Department at (847) 938-9898.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

48

9.5.4 Safety Procedures

9.5.4.1 Adverse Events

An adverse event is defined as any unexpected event(s) such as sign(s), symptom(s), and/or laboratory finding(s) associated with the use of drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the patient after study randomization in this study.

The patient will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken.

All adverse events whether in response to a query, observed by site personnel, or spontaneously reported by the patient will be reported on the appropriate CRF.

All adverse events and post-treatment laboratory abnormalities considered clinically significant by the investigator will be followed to a satisfactory resolution.

The investigator will assess and record any adverse event in detail on the adverse events CRF including the date and time of onset, description, severity, intermittence, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as intermittent or continuous, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

- | | |
|-----------|---|
| Mild: | The adverse event is transient and easily tolerated by the patient. |
| Moderate: | The adverse event causes the patient discomfort and interrupts the patient's usual activities. |
| Severe: | The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening. |

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

49

The investigator will use the following definitions to assess the relationship of the adverse event to the use of the study drug:

- Probable: An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
- Possible: An adverse event has a strong temporal relationship to study drug and an alternate etiology is equally or less likely compared to the potential relationship to study drug. If possibly related, an alternative etiology must be provided.
- Probably Not: An adverse event has little or no temporal relationship to the study drug and/or more likely alternative etiology exists. If probably not related, an alternative etiology must be provided.
- Not Related: An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e. g., has no temporal relationship to study drug or has a much more likely alternative etiology). If not related, an alternative etiology must be provided.

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

Since measurements of pain intensity are efficacy measurements in this study, any change in pain intensity due to the underlying pain state under study will not be considered adverse events for the purposes of this study. In addition, anticipated peri-operative events following molar extraction surgery, such as swelling or edema, hematoma,

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

50

bleeding, dry socket, nerve injury, oral-antral communication (sinus exposure), infection, decrease in mandibular range of motion, soreness with mandibular movement, and bruising, will not be captured as adverse events in this study. If, in the opinion of the investigator, the peri-operative event is of a greater degree than routinely associated with molar extraction surgery, then the event will be recorded as an adverse event.

9.5.4.2 Serious Adverse Events

A serious adverse event is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above, i.e., death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or congenital anomaly/birth defect. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone and provide a written account of the event to one of the following people at Abbott Laboratories within 24 hours of being aware of any serious adverse event (SAE).

Rita M. Driscoll, M. D.
 Associate Medical Director
 Analgesia Venture
 Dept. 42D, Bldg. AP34
 200 Abbott Park Road

Christopher J. Silber, M. D.
 Venture Head
 Analgesia Venture
 Dept. 42D, Bldg. AP34
 200 Abbott Park Road

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

51

Abbott Park, Illinois 60064-3500
 Office: (847) 938-7966
 Fax: (847) 937-9197

Abbott Park, Illinois 60064-3500
 Office: (847) 938-5236
 Home: (847) 615-0428
 Fax: (847) 938-5258

If the Abbott Medical Monitors listed above cannot be contacted, the event must be reported to one of the Abbott Personnel listed below within 24 hours of discovery. The Abbott personnel will then be responsible for reporting this information to the Abbott Medical Monitor and other appropriate Abbott personnel.

Renee Reitmayer
 Sr. Clinical Research Associate
 Analgesia Venture
 Dept. 48Q, Bldg. AP34
 200 Abbott Park Road
 Abbott Park, Illinois 60064-3500
 Office: (847) 938-5887
 Home: (847) 395-4628
 Fax: (847) 938-5258

Bruce McCarthy, M.D.
 Associate Medical Director
 Analgesia Venture
 Dept. 48Q, Bldg. AP34
 200 Abbott Park Road
 Abbott Park, Illinois 60064-3500
 Office: (847) 935-6244
 Home: (847) 855-8523
 Fax: (847) 938-5258

9.5.5 Appropriateness of Measurement

All clinical, laboratory, and pain assessment procedures to be used in this study are standard and generally accepted.

9.5.6 Primary Efficacy Variables and Criteria for Evaluability

The primary efficacy variable in this study will be TOTPAR score. Secondary efficacy variables will include the SPID scores for both categorical scale and VAS, SPRID, the time to patient's first noticeable pain relief (i.e., onset of pain relief), the time to the patient's first meaningful pain relief (i.e., 50% reduction in pain from baseline), the time to rescue medication, the proportion of patients experiencing meaningful pain relief after dosing, and the patient's global evaluation.

CONFIDENTIAL INFORMATION ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

52

All the time-interval-weighted pain scores (TOTPAR, SPID, SPRID) will be calculated through the first six hours after study drug administration. The time to the patient's first noticeable pain relief and first meaningful pain relief will be measured through the first six hours of study drug administration while the time to rescue medication will be recorded through the first 24 hours after study drug administration.

9.5.7 Drug Concentration Variables

The variables will include maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) for 24 hours. Noncompartmental methods will be used to obtain the AUC value, using the linear trapezoidal rule. Other pharmacokinetic parameters may be calculated if useful and appropriate.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the principal investigator and his essential personnel, including the study coordinator and pharmacist. This meeting will entail a discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel will be trained on the study procedures by an Abbott monitor at the study initiation visit. The Abbott monitor will monitor the site as deemed necessary. At each visit, 100% source document review will be made against the entries on the CRFs and a quality assurance check will be performed to ensure that the investigator is complying with protocol and regulations. In addition, once CRFs are retrieved by the Abbott monitor, a review of the data will be conducted by an Abbott Laboratories' physician and a clinical review team.

All case report forms must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the case report forms for completeness and accuracy and sign and date the set of case report forms where indicated. Case report forms will be reviewed periodically for completeness, legibility, and acceptability by Abbott Laboratories

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

Part 5

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

53

personnel (or their designee) and the investigator (or designee) at the study site. The investigator must agree to provide Abbott (or designee) access to all source documents in order to verify case report forms.

Data will be entered into the mainframe computer by a double-key entry procedure at Abbott Laboratories. Clinical laboratory data will be electronically transferred from the central laboratory. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary corrections will be made to the database and documented.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests will be two-tailed and considered statistically significant if the p-value (type one error rate) is less than or equal to 0.05 (when rounded to three decimal places).

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons will be made as considered necessary.

Baseline value for all variables is defined at the last value obtained prior to receiving study drug.

9.7.1.1 Data Sets Analyzed

Efficacy analyses will be performed for two sets of data: intent-to-treat patients and evaluable patients, as defined in accordance with Sections 9.3.1 and 9.3.2. Patients receiving study drug with at least one postdosing pain assessment will be included in the intent-to-treat analyses. Classification of patients regarding acceptability of data for evaluable efficacy analyses will be carried out by the project team (clinical, data

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

54

management, and statistics) prior to their knowledge of double-blind treatment assignment. Safety analyses will be performed with all randomized patients who receive study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the six treatment groups. Comparability among the treatment groups will be assessed by a one-way analysis of variance (ANOVA), with treatment group as the main effect for quantitative variables, and by Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

The primary efficacy variable in this study will be TOTPAR score. Secondary efficacy variables will include the SPID scores for both categorical scale and VAS, SPRID, the time to patient's first noticeable pain relief (i.e., onset of pain relief), the time to patient's first meaningful pain relief (i.e., 50% reduction in pain from baseline), the time to rescue medication, the proportion of patients experiencing meaningful pain relief after dosing, and the patient global evaluation. All measures of efficacy are derived from the patient pain assessments recorded in the presence of a trained site observer.

For patients taking rescue medication greater than 1.5 hours but less than 6 hours after dosing or who are withdrawn from the study for any other reason in this timeframe, the pain score last recorded will be carried forward for subsequent time evaluations. The secondary efficacy variables, time to first noticeable pain relief and first meaningful pain relief, within six hours after dosing will be considered censored at six hours and time to rescue medication will be censored at 24 hours. The information obtained from the pain assessments completed at 12 and 24 hours after study drug administration will be collected for informational purposes and utilized for the development of future study designs.

The time-interval-weighted pain scores will be calculated through the first six hours after study drug administration. The TOTPAR, SPID, and SPRID scores will be analyzed using analysis of variance techniques with appropriate models. Regression

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

55

analysis will be used to assess dose response, both with and without placebo. The time to the patient's first meaningful pain relief and the time to rescue medication will be analyzed by using nonparametric survival models. Log rank statistics will be used to compare the treatment groups. The proportion of patients experiencing meaningful pain relief from baseline will be compared pairwise among the treatment groups by Fisher's exact test. The final global evaluation score will also be compared among the treatment groups using Cochran-Mantel-Haenszel methodology for ordered response variables.

The effect of study segment will be assessed by comparing data from the two segment groups within the placebo and ibuprofen treatment groups. If there is no statistically significant effect of segment, then data from the two segment groups will be pooled within the placebo and ibuprofen treatment groups. However, if there is a significant effect of segment, then an appropriate term will be introduced to the statistical models. The efficacy variables will be also analyzed by stratifying for nicotine use and the pain severity at baseline before the dosing. The effect of sex on treatment group differences will be assessed, if necessary.

An interim administrative analysis for this study may be performed, which would be distinct from the planned blinded safety assessment to be performed between dosing segments. The results of such an administrative analysis would be used solely for planning subsequent studies of ABT-594, and should not be used to alter this ongoing study. Accordingly, no adjustment to the Type I error rate would be made.

Other analyses, if appropriate, will be performed.

9.7.1.4 Safety

All patients receiving study medication will be evaluated for safety.

Adverse events will be coded using the COSTART V^s dictionary. Treatment-emergent adverse events will be tabulated by body system and COSTART term for each treatment group. Pairwise comparisons between treatment groups will be made using Fisher's exact test for the proportion of patients reporting a particular adverse event. Analyses by subgroup will be performed; specifically, analysis by sex and nicotine use will be performed.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

56

Laboratory data will be analyzed using a one-way ANOVA with treatment as the main effect. Baseline comparability among treatment groups will be assessed by the overall F-test of the one-way ANOVA. The primary analyses will be on the change from baseline to the minimum, maximum, and final value during the study for each laboratory variable.

Additionally, laboratory data will be categorized as low, normal, or high based on the normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory values which satisfy the criteria for potentially clinically significant laboratory values (Appendix E) will be identified.

Vital signs and ECG parameters considered potentially clinically significant (Appendix E) will be noted in the report. Changes in vital signs from baseline will be analyzed using a one-way ANOVA with the treatment as the main effect. If it is indicated, additional exploratory safety analyses will be performed.

9.7.1.5 Pharmacokinetics

The hypothesis of invariance with dose will be tested for dose-normalized C_{max} and dose-normalized AUC. If the probability distribution appears to have nonsymmetry that is notably reduced by a transformation, the analysis will be performed on transformed data. The hypothesis of invariance with dose and no effect of nicotine user will be tested within the framework of an analysis of covariance with a patient classified by study segment, by nicotine use (non-user or user), and by dose level (lower or higher). All two-way and three-way interactions between these three factors will initially be included in the model; however, if interactions involving the nicotine use factor appear to be of little importance, they will be dropped from the model. Body weight will be a covariate and other covariates such as sex may also be included.

If there is evidence of an analgesic effect, the relationship between the effect and drug concentration will be explored with nicotine use category and other variables accounted for as appropriate. For overall efficacy variables such as TOTPAR and SPID, the

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

57

relationship with C_{max} and AUC will be explored. In addition, mixed effect models may be used to explore the relationship of drug concentration with pain relief and VAS values at individual times of assessment.

If appropriate and useful, other analyses may be performed.

9.7.2 Determination of Sample Size

This study is designed to enroll approximately 288 patients (48 patients in each treatment group). This sample size allows for the detection of significant differences in SPID and TOTPAR between ABT-594 and placebo at $p = 0.05$ (two-tailed) level with at least 70% power, assuming that ABT-594 provides pain relief equal to that of acetaminophen plus codeine. If ABT-594 is as efficacious as ibuprofen 400 mg, the power will exceed 70%. Calculations are based on the following results obtained from various published dental pain studies similar to this study.

	Median of Means: Acetaminophen plus Codeine	Median of Means: Ibuprofen	Median of Means: Placebo	Pooled Standard Deviations
SPID	4.1	5.75	1.2	5.0
TOTPAR	9.3	13.50	4.9	5.5

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

This study will be conducted in accordance with the protocol, GCP, all applicable local, state, federal regulations and regulatory requirements. The protocol will not be modified by the investigator without first obtaining the concurrence of the sponsor. Abbott Laboratories will notify the investigator of any protocol modifications. Protocol modifications will be confirmed in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the patient or those of an administrative or clarifying nature, must be reviewed and approved by the IRB before implementation.

This study will be terminated if these conditions are not met.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

58

10.0 Protocol Deviation

When significant deviation from the protocol is deemed necessary for an individual patient, the investigator or other physician in attendance must contact the Abbott monitor (listed in Section 9.5.4.2). Such contact will be made as soon as possible to permit a decision as to whether or not the patient is to continue in the study. Any departures from the protocol and the reason for it will be recorded on the case report form. The reason for such a joint decision must be documented in writing.

11.0 Use of Information and Publication

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with completed test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, and not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 30 days before the date of submission to the intended publisher.

12.0 Completion of the Study

The investigator will complete and report this study in satisfactory compliance with the protocol within nine months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon the writing by both the investigator and

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

59

Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigation product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as the when these documents no longer need to be retained.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

60

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

61

14.0 References

1. American Academy of Pain Medicine (1997). The Use of Opioids for the Treatment of the Treatment of Chronic Pain. Pp. 1-4.
2. Twycross R. Pain Relief in Advanced Cancer. Churchill Livingstone, Endinburgh, 1994.
3. Sullivan JP and Bannon AW. Epibatidine: pharmacologic properties of a novel nicotinic acetylcholine agonist and analgesic agent. *CNS Drug Rev.* 2(1):21-39, 1996.
4. Sullivan JP, Briggs CA, Donnelly-Roberts D, Brioni JD, Radek RJ, McKenna DG, Campbell JE, Arneric SP, Decler MW, Bannon AW. (\pm)-Epibatidine can differentially evoke responses mediated by putative subtypes of nicotinic acetylcholine receptors (nAChRs). *Med Chem Res.* 4:502-516; 1994.
5. "COSTART" Coding Symbols for Thesaurus of Adverse Reaction Terms: Fifth Edition, Department of Health and Human Services, Food and Drug Administration, Rockville, MD.

IN/R-S/2/Folder ABT594/Folder 97772/97772A2/9.5.1.1

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

62

Appendix A

Responsibilities of the Clinical Investigator

1. To conduct the stud(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of patients.
2. To personally conduct or supervise the described investigation(s).
3. To inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent in 21 CFR¹ Part 50 and IRB review and approval in 21 CFR Part 56 are met.
4. To report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
5. To read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
7. To maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
8. To ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. To also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human patients or others. Additionally, will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human patients.
9. To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

1. Code of Federal Regulations, Food and Drugs. Office of the Federal Register, National Food and Drugs Archives and Records Administration. U.S. Government Printing Office, Washington, D.C., 1989.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

63

Appendix B

Elements of an Informed Consent

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

IND Studies - Procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all subjects participating in PPD Clinical Research studies or the subjects' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of subjects involved in the trial.
4. The expected duration of the subject's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The subject's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the subject and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the subject for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the subject, this should be stated.

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

64

13. The anticipated prorated payment, if any, to the subject for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
15. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research subject's rights (ideally not the investigator).
19. Whom to contact if the event of trial-related injury of the subject.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the subject or the subject's legally acceptable representative is authorizing such access.
21. A statement that the confidential follow-up form (Form 00) will be retained by Abbott, if applicable.
22. A statement that the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identify will remain confidential.
23. The foreseeable circumstances and/or reasons under which the subjects' participation in the trial may be terminated.
24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the subject may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the consent is given to the subject.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

65

29. The statement, "I agree to participate..."
30. A place for the subject or the subject's legally acceptable representative to sign and date.
31. A place for the signature and date of the person who conducted the informed consent discussion.

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

66

Appendix C

Pain Assessments

Only the Pain Intensity Categorical and VAS Scales are assessed and recorded at baseline (0 hour). All of the following measurements of pain will be assessed and recorded at the time points specified in Section 9.5.2.

Pain Intensity Categorical Scale

The patient's pain intensity will be assessed by completion of the following statement.

My pain at this time is:

- 0 None
- 1 Mild
- 2 Moderate
- 3 Severe

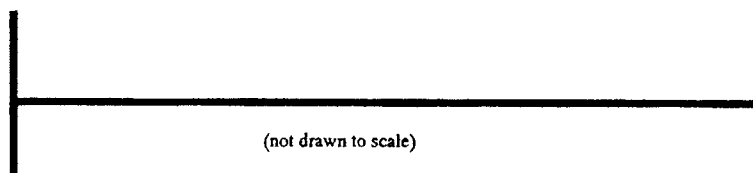
Pain Intensity Visual Analog Scale (VAS)

The patient will place a line on the VAS of the patient pain assessment worksheet to indicate the magnitude of his/her pain.

My pain at this time is:

No Pain

Worst Pain



Using a standard ruler supplied by SCIREX, site personnel will measure the distance in millimeters (0-100 mm) from the left side of the scale to the patient's vertical mark and record this number on the appropriate CRF page. The patient pain assessment worksheet

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

67

will be retained at the site as part of source documentation. The patient should be reminded that each assessment should be performed independently of previous assessments.

Pain Relief Categorical Scale

The patient's pain relief will be assessed by completion of the following statement.

My relief from starting pain is:

- 0 None
- 1 A little
- 2 Some
- 3 A lot
- 4 Complete

Stopwatch Model

The patient will be given two stopwatches and the study nurse will have one stopwatch. All three stopwatches will be started at the same time, immediately after the study drug has been administered (this is baseline). One of the patient's stopwatches will be labeled "perceptible or noticeable" and the 2nd stopwatch will be labeled "meaningful." The nurse's instructions are as follows:

Step 1: Objective is to determine the initial onset of action of the study medication.

Tell the patient "When you first notice (or perceive) any relief from the study medication, stop the stopwatch (show them how). Before you stop the watch you need to be sure that you really notice a reduction in your pain level. (When possible) This should be a reduction of at least 1 number on the Visual Analog Scale (show them where on the VAS). If

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

68

you feel you have achieved this pain level, stop the watch and bring it to me.

Step 2: Objective is to determine when the patient first feels that their relief is meaningful.

Tell the patient "When you feel your relief from the study medication is meaningful, that is when your relief is meaningful to you, stop the watch (show them how). (When possible) This should be a reduction from your starting pain of at least one-half (show them where on the VAS). If you feel you have achieved this pain level, stop the watch and bring it to me."

Remind the patient at each of the regularly scheduled assessment times to be sure and stop the watches when they notice any relief and when they feel that they have had meaningful relief if they have not returned the watches previously.

Patient Global Evaluation

At 6 hours after study drug administration or upon premature termination or prior to receiving analgesic rescue medication, if these latter two events occur less than six hours after study drug administration, the patient's overall impression (global evaluation) of the analgesic relief due to study drug will also be obtained. The patient will be asked the following question and requested to record the time at which it was answered:

"How would you rate the study medication you received for pain?"

- 4 Excellent
- 3 Good
- 2 Fair
- 1 Poor

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

69

Appendix D

Instructions for the Collection and Handling of Blood Samples

1. Insert and indwelling catheter or make direct venipuncture from the antecubital vein with a 21 gauge needle.
2. Collect blood into a chilled Becton-Dickinson green-top Vacutainer[®] containing sodium heparin (provided by SCIREX).
3. Gently invert the Vacutainer[®] four times to mix the anticoagulant with the collected blood prior to centrifugation and immediately place it on ice.
4. Centrifuge the Vacutainers[®] for 10 minutes at approximately 1200 x g at 4°C in a refrigerated centrifuge.
5. Gently remove the plasma from the packed cells immediately following centrifugation. Separate plasma and transfer to a cryotube labeled with the appropriate label (provided by SCIREX).

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

70

Appendix E
Potentially Clinically Significant Values for Laboratory
Determinations, Vital Signs and Electrocardiogram Variables

Hematology	Very Low	Very High
Hemoglobin (g/dL)		
Female	≤ 9.5	≥ 16.5
Male	≤ 11.5	≥ 18.5
Hematocrit (%)		
Female	≤ 32	≥ 50
Male	≤ 37	≥ 55
Red Blood Cells ($\times 10^{12}/L$)		
Female	≤ 3.5	≥ 6.0
Male	≤ 3.8	≥ 7.0
White Blood Cells ($\times 10^9/L$)	≤ 2.8	≥ 16.0
Platelet Count ($\times 10^9/L$)	≤ 75	≥ 700
Eosinophils (%)		≥ 10
Basophils (%)		≥ 10
Lymphocytes (%)		≥ 75
Monocytes (%)		≥ 15
Neutrophils (%)	≤ 15	
Bands (%)		≥ 10
Mean Corpuscular Volume (fL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Mean Corpuscular Hemoglobin Concentration (g/dL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Atypical Lymphocytes (%)		≥ 5
Prothrombin Time (sec)		$\geq 2 \text{ ULN}$
Partial Thromboplastin Time (sec)		$\geq 2 \text{ ULN}$

LLN = Lower limit of normal ULN = Upper limit of normal

CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

71

Chemistry	Very Low	Very High
Albumin (g/dL)	≤ 2.5	
Alkaline Phosphatase (IU/L)		$\geq 3 \times \text{ULN}$
Bicarbonate (mEq/L)	≤ 12	≥ 38
BUN (mg/dL)		≥ 30
Calcium (mg/dL)	≤ 8.2	≥ 12
Chloride (mEq/L)	≤ 90	≥ 118
Cholesterol (mg/dL)		≥ 600
Creatinine (mg/dL)		≥ 2.0
Direct Bilirubin (mg/dL)		≥ 2.0
Glucose (mg/dL)	≤ 45	≥ 175
LDH (IU/L)		$\geq 3 \times \text{ULN}$
Inorganic Phosphorus (mg/dL)	≤ 1.7	≥ 5.5
Potassium (mEq/L)	≤ 3.0	≥ 6.0
SGOT/AST (IU/L)		$\geq 3 \times \text{ULN}$
SGPT/ALT (IU/L)		$\geq 3 \times \text{ULN}$
Sodium (mEq/L)	≤ 126	≥ 156
Total Bilirubin (mg/dL)		≥ 2.0
Total Protein (g/dL)	≤ 4.5	≥ 10
Triglycerides (mg/dL)		≥ 600
Uric acid (mg/dL)		
Female		≥ 8.5
Male		≥ 10.5

ULN = Upper limit of normal

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

72

Urinalysis	Very Low	Very High
Specific Gravity	≤ 1.001	≥ 1.030
PH	≤ 4	≥ 9
Protein		$\geq 3+^*$ (≥ 10)
Ketones		$\geq 3+^*$
RBC		
Female		$\geq 10/\text{hpf}$
Male		$\geq 8/\text{hpf}$
WBC		$\geq 10/\text{hpf}$ ($\geq 2+$)
Casts		≥ 9
Glucose		$\geq 3+^*$
Oral Body Temperature		
Temperature	Low: decreased $\geq 2^\circ\text{F}$ from baseline High: $\geq 101^\circ\text{F}$ and increased $\geq 2^\circ\text{F}$ from baseline	
Body Weight		
Weight	Low: decreased $\geq 15\%$ from baseline High: increased $\geq 15\%$ from baseline	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mmHg and decreased ≥ 30 from baseline High: ≥ 180 mmHg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mmHg and decreased ≥ 20 from baseline High: ≥ 105 mmHg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	
Orthostatic Vital Signs		
Systolic Blood Pressure	Low: ≤ 86 mmHg and decreased ≥ 30 from supine	
Heart rate	High: ≥ 130 bpm and increased ≥ 20 bpm from supine	

* $\geq 3+$ on a scale with 4+ being the maximum value

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
 Protocol M97-772
 Incorporating Amendments One and Two - June 22, 1998

73

Electrocardiogram	
PR Interval	High: ≥ 210 msec
QRS Duration	Low: ≤ 50 msec
	High: ≥ 150 msec
QT Interval	Low: ≤ 200 msec
	High: ≥ 500 msec
QTc Interval [#]	Low: ≤ 200 msec
	High: ≥ 500 msec
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline

[#] QTc calculated as QT divided by the square root of RR interval

**CONFIDENTIAL INFORMATION
 ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ABT-594
Protocol M97-772
Incorporating Amendments One and Two - June 22, 1998

74

Attachment I Sample Abbott Laboratories Drug Inventory Form

Study Number: M97-772Investigator: Dr. Stephen Daniels

Drug (s): _____

Date Received: _____

Quantity Verified by: _____

Lot #s: _____

SME (Shipping Memorandum Export) #: _____

Quantity Received:

NPRO #:

[illegible]

* Site Pharmacist ** Designated site personnel @ Abbott Monitor

**CONFIDENTIAL INFORMATION
ABBOTT LABORATORIES**

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

6668-R2

ORIGINAL INVESTIGATION

Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain

Placebo-Controlled Trial and Long-term Evaluation

Sanford H. Roth, MD; Roy M. Fleischmann, MD; Francis X. Burch, MD; Frederick Dietz, MD; Barry Bockow, MD; Ronald J. Rapoport, MD; Joel Rutstein, MD; Peter G. Lacouture, PhD

Background: Although opioid analgesics have well-defined efficacy and safety in treatment of chronic cancer pain, further research is needed to define their role in treatment of chronic noncancer pain.

Objective: To evaluate the effects of controlled-release oxycodone (OxyContin tablets) treatment on pain and function and its safety vs placebo and in long-term use in patients with moderate to severe osteoarthritis pain.

Methods: One hundred thirty-three patients experiencing persistent osteoarthritis-related pain for at least 1 month were randomized to double-blind treatment with placebo (n = 45) or 10 mg (n = 44) or 20 mg (n = 44) of controlled-release oxycodone every 12 hours for 14 days. One hundred six patients enrolled in an open-label, 6-month extension trial; treatment for an additional 12 months was optional.

Results: Use of controlled-release oxycodone, 20 mg, was superior ($P < .05$) to placebo in reducing pain inten-

sity and the interference of pain with mood, sleep, and enjoyment of life. During long-term treatment, the mean dose remained stable at approximately 40 mg/d after titration, and pain intensity was stable. Fifty-eight patients completed 6 months of treatment, 41 completed 12 months, and 15 completed 18 months. Common opioid side effects were reported, several of which decreased in duration as therapy continued.

Conclusions: Around-the-clock controlled-release oxycodone therapy seemed to be effective and safe for patients with chronic, moderate to severe, osteoarthritis-related pain. Effective analgesia was accompanied by a reduction in the interference of pain with mood, sleep, and enjoyment of life. Analgesia was maintained during long-term treatment, and the daily dose remained stable after titration. Typical opioid side effects were reported during short- and long-term therapy.

Arch Intern Med. 2000;160:853-860

From Arthritis Center Ltd, Phoenix, Ariz (Dr Roth); Rheumatology Associates, Metroplex Clinical Research Center, Dallas, Tex (Dr Fleischmann); Rockford Clinic, Rockford, Ill (Dr Dietz); Truesdale Clinic, Fall River, Mass (Dr Rapoport); Arthritis Diagnostic and Treatment Center, San Antonio, Tex (Dr Rutstein); and Purdue Pharma LP, Norwalk, Conn (Dr Lacouture). Dr Burch is in private practice in San Antonio, and Dr Bockow is in private practice in Seattle, Wash. Dr Roth is now with ArthroCare, Arthritis Care & Research, PC, Phoenix. Dr Lacouture is employed by Purdue Pharma LP, the manufacturer of controlled-release oxycodone tablets (OxyContin tablets).

OSTEOARTHRITIS is one of the most common joint disorders, with radiographic evidence of the disease present in most of the population by age 65 years and in 80% of the population by age 75 years.¹ Pain associated with osteoarthritis contributes substantially to disability² and has a negative impact on motor function, sleep, and mood.³ Thus, control of pain is an important goal of therapy.^{4,5} Frequently prescribed oral analgesics include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), combinations of an opioid with aspirin or acetaminophen, and tramadol hydrochloride.^{2,6} Use of nonopioid analgesics to treat moderate to severe osteoarthritis pain is limited by a ceiling effect for analgesia⁷ and potential toxic effects at high doses,^{8,9} with gastrointestinal tract, hepatic, and renal side effects of NSAID

use of particular concern in elderly patients.^{9,10}

The need to find effective strategies for managing chronic, moderate to severe noncancer pain has led to the reappraisal of opioids for this use. The favorable experience with long-term administration of centrally acting opioid analgesics to treat cancer pain¹¹⁻¹³ suggests that opioid treatment would be effective in noncancer pain as well. However, the clinical literature regarding long-term use of opioids for the management of chronic noncancer pain is contradictory. Some studies,¹⁴⁻¹⁹ usually from populations at multidisciplinary pain clinics, have associated opioid use with functional impairment, increased pain, central nervous system (CNS) toxic effects, and drug abuse. Other studies²⁰⁻²⁵ describe favorable experiences with opioid use in some patients, including effective analgesia, no CNS toxic effects, im-

PATIENTS AND METHODS

One hundred thirty-three adults with persistent osteoarthritis-related pain for at least 1 month and moderate or severe pain at baseline were enrolled in the placebo-controlled trial. The diagnosis of osteoarthritis was confirmed by the following criteria: (1) at least a 3-month history of 2 or more of the following clinical signs—pain aggravated by motion and at least partly relieved by rest, limitation of the range of motion, stiffness with inactivity, bony tenderness on pressure, bony swelling, and joint fluid analysis consistent with osteoarthritis if effusion was present; and (2) at least 1 of the following radiographic findings—osteophytes, joint space narrowing, subchondral bony sclerosis, or bony cysts. Patients with severe organ dysfunction were excluded, as were those with a history of drug or alcohol abuse. Patients taking NSAIDs could continue their use if the dose had been stable for 1 month at the maximum dose tolerated by or effective for the patient and if the dose would not be changed. Use of other analgesics was prohibited throughout the study, and use of opioid analgesics was discontinued at study entry. One hundred six patients who had participated in the placebo-controlled trial were enrolled in the long-term, open-label extension trial. Each of the 7 participating rheumatology clinics obtained institutional review board approval before each study was initiated, and written informed consent was obtained from each patient before enrollment into either trial.

STUDY DESIGN

Placebo-Controlled Trial

At baseline, patients were randomly assigned to 1 of 3 double-blind treatment groups: placebo or 10 mg or 20 mg of CR oxycodone every 12 hours (q12h). Each patient received 2 bottles, each containing identical placebo or 10-mg CR oxycodone tablets (OxyContin tablets; Purdue Pharma LP, Norwalk, Conn). The treatment was concealed in a tear-off portion of the label, which was stapled to the patient's

case report form, and the masked status was maintained until the study database was complete and prepared for analysis. One tablet was taken from each bottle at 8 AM and 8 PM daily for 14 days. Dose titration and use of rescue analgesia were prohibited.

Each day, patients rated night, morning, afternoon, and evening pain intensity using a 4-point categorical scale (0 indicates none; 1, slight; 2, moderate; and 3, severe). This scale is the most widely used,²⁸ is simple for patients to use, is a valid indicator of pain intensity, and correlates well with other measures of pain intensity.²⁹ Patients also evaluated quality of sleep using a 5-point scale from 1 (very poor) to 5 (excellent).

At baseline, week 1, and week 2, patients completed the Brief Pain Inventory,³⁰ rating their worst, least, and average pain "in the last 24 hours" and pain "right now" using a numerical scale from 0 (no pain) to 10 (pain as bad as you can imagine). Numerical scales were used to rate interference of pain (0 indicates does not interfere; 10, completely interferes) on key functional activities and emotions: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.³¹ Patients also completed an activities and lifestyle questionnaire in which they rated their ability to perform 8 daily activities (dress yourself, get in and out of bed, lift cup or glass to mouth, walk outdoors, wash and dry entire body, bend down, turn faucets, and get in and out of the car) using a 4-point categorical scale from 1 (without any difficulty) to 4 (unable to do) (modified from Pincus et al³²).

Adverse experiences spontaneously reported by patients or observed by the investigators were recorded at each visit. All patients underwent baseline and end-of-study laboratory evaluations and physical examinations, during which vital signs were recorded.

Long-term Extension Trial

Patients who had participated in the placebo-controlled trial were eligible for an open-label 6-month extension trial. Two optional 6-month extension trials were added by protocol amendments, providing a maximum possible duration of

proved performance in some cases, and only infrequent instances of abuse, when opioid analgesics were included as part of a comprehensive, individualized pain management program.

Few blind, placebo-controlled clinical trials have evaluated the efficacy of opioid therapy in chronic non-cancer pain. One double-blind, 7-day, placebo-controlled crossover study²⁶ (with subsequent 19-week open evaluation) found that controlled-release (CR) codeine administration reduced pain and pain-related disability in patients with chronic nonmalignant pain, 43.3% of whom had rheumatic pain. Another randomized, double-blind, 9-week crossover study²⁷ compared CR morphine sulfate therapy with active placebo use in patients with treatment-resistant chronic regional soft tissue or musculoskeletal pain. Opioid therapy reduced pain intensity but with no functional or psychological improvement. No impairment of cognitive function and no drug-seeking behaviors were observed. Thus, results of these 2 double-blind, placebo-controlled trials supported the

analgesic effect of opioid use in chronic nonmalignant pain but did not focus on long-term effectiveness and safety.

The present studies were undertaken to assess the effectiveness of an oral CR formulation of the opioid oxycodone for the short- and long-term treatment of moderate to severe pain associated with osteoarthritis. A randomized, double-blind, parallel-group study compared the analgesic efficacy, effect on function, and safety of 2 dose levels of CR oxycodone with placebo. An open-label extension trial assessed analgesic effectiveness, need for dose adjustments, effect on function, and safety during long-term treatment with CR oxycodone.

RESULTS

PLACEBO-CONTROLLED TRIAL

Patients with moderate to severe osteoarthritis-related pain were randomized to double-blind treatment with pla-

18 months. All patients received CR oxycodone tablets q12h at approximately 8 AM and 8 PM. The minimum dose was 10 mg q12h, and the dose was titrated until adequate pain control was achieved with an acceptable level of side effects. The q12h doses could be titrated symmetrically (ie, same dose in the morning and in the evening) or asymmetrically (ie, higher dose in the morning or in the evening), depending on the patient's need for pain control during the day.

Clinic visits were scheduled at baseline and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 64, and 72. Patients were contacted by telephone daily during the first week of the trial, once a week until week 24, then when considered necessary by the investigator. The continuing need for opioid analgesia therapy was assessed by means of scheduled respite from opioid therapy, which began at the end of the clinic visits at weeks 4, 8, 16, 24, 48, and 64. Patients resumed CR oxycodone treatment if they reported that their pain intensity was unacceptable. Pain intensity, quality of sleep, and the number of night awakenings due to pain were assessed at baseline and at weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 72. The activities and lifestyle questionnaire was administered at baseline and at weeks 4, 24, 32, 40, 48, 56, 64, and 72. All adverse events spontaneously reported by patients or observed by the investigators were recorded. Physical examinations (including vital signs) and laboratory evaluations were performed at baseline and at the end of the study for each patient. After the last visit, the investigators telephoned the patients daily until the patient reported unacceptable moderate to severe pain. The patient was then instructed to resume therapy prescribed by his or her physician.

STATISTICAL ANALYSIS

In the placebo-controlled trial, the primary efficacy variable was mean pain intensity calculated from patients' daily categorical scores. This was analyzed for the population of patients who took at least 4 doses of study medication, recorded at least 2 pain intensity evaluations, and complied with the protocol ($n = 109$). For this analysis, missing

values were replaced by the last set of observations for that patient. For the remaining efficacy variables and all safety variables, all patients enrolled in the study ($N = 133$) were included in the statistical analyses (intent to treat).

Baseline demographics were analyzed using a Cochran-Mantel-Haenszel test for categorical variables and analysis of variance (ANOVA) for continuous variables. An analysis of covariance (ANCOVA), with baseline pain intensity as a covariate, was used for weekly and overall pain intensity. Models encompassed treatment, study center, sex, age (<65 or ≥ 65 years), and intervariable interactions. The Dunnett test was performed to compare active treatments with placebo, regardless of the significance level of the overall ANCOVA. The least significant difference test was used to compare the 2 active treatments if the overall ANCOVA was statistically significant. Activities and lifestyle questionnaire and Brief Pain Inventory responses were analyzed using either ANOVA or logistic regression, depending on the level of measurement of the variable. The dependent variables of the ANOVA were in terms of change from baseline. In all of the ANOVA and ANCOVA models, least squares means for the response variables were also calculated. The χ^2 test was performed to compare the difference between the active groups and the placebo group for discontinuations due to lack of efficacy and adverse events. Logistic regression was used to analyze treatment effects associated with adverse events. The model contained treatment, center, sex, and age.

In the long-term open-label trial, an overall trend analysis was performed from week 2 to the end of the study for pain intensity and "duration ratio" of the 4 most common opioid-related side effects (nausea, pruritus, somnolence, and constipation) using a mixed effects model with random intercept and slope. Duration ratio was calculated as the number of days the patient experienced the adverse event divided by the number of days the patient was treated with CR oxycodone, expressed as a percentage.

All statistical tests were 2 sided, with a significance level of $P = .05$ for main effects and $P = .10$ for interaction terms. Results are presented as mean (SE).

cebo ($n = 45$) or 10 mg ($n = 44$) or 20 mg ($n = 44$) of CR oxycodone q12h (**Table 1**). There were no statistically significant differences among treatment groups in baseline characteristics. Most patients (73.7%) were women. The average age of patients was 62 years, and 42.9% were 65 years or older. The most common osteoarthritic sites were the spine or back (45.9%) and the knee (30.8%). Most patients had chronic disease, with an average duration of 9 years. Eighty-one patients (60.9%) had been taking opioid analgesics, which were discontinued before enrollment; 78 of these patients had been receiving fixed-combination products. Eighty-seven patients (65.4%) continued taking NSAIDs throughout the study.

Seventy patients (52.6%) discontinued study participation prematurely (**Figure 1**), 39 because of ineffective treatment and 28 because of adverse experiences (predominantly nausea, vomiting, and somnolence). The number of patients discontinuing for ineffective treatment was significantly lower in the active groups than in the placebo group: 22 in the placebo group, 12 in the

10-mg q12h group ($P = .04$ vs placebo), and 5 in the 20-mg q12h group ($P < .001$ vs placebo). The number of patients discontinuing for adverse events was significantly higher in the active groups than in the placebo group: 2 in the placebo group, 12 in the 10-mg q12h group ($P = .009$ vs placebo), and 14 in the 20-mg q12h group ($P = .004$ vs placebo). Of the remaining 3 patients who discontinued, all in the placebo group, 1 withdrew consent and 2 took analgesics prohibited by the protocol.

In many analgesic trials, a 20% average reduction in baseline pain intensity is considered clinically meaningful. Based on the 4-point categorical scale, use of 20 mg of CR oxycodone q12h attained this goal within 1 day, and use of 10 mg of CR oxycodone q12h attained this goal by day 2; the placebo group never achieved this reduction (**Figure 2**). The reduction in pain intensity with use of 20 mg of CR oxycodone q12h was prompt and sustained: taking 20 mg of CR oxycodone was more effective ($P < .05$) in reducing mean pain intensity at weeks 1 and 2 and overall than was taking placebo or 10 mg of

Table 1. Characteristics of 133 Patients Enrolled in the Placebo-Controlled Trial*

Characteristic	Placebo Group (n = 45)	CR Oxycodone q12h Group	
		10 mg (n = 44)	20 mg (n = 44)
Sex, M/F	10/35	13/31	12/32
Age, y			
Mean (SE)	62 (2)	62 (2)	63 (2)
Range	32-85	38-81	41-90
<65, No. (%)	27 (60)	25 (57)	24 (55)
≥65, No. (%)	18 (40)	19 (43)	20 (45)
Baseline pain intensity, mean (SE)†	2.4 (0.1)	2.5 (0.1)	2.4 (0.1)
Osteoarthritis site, No. (%)			
Spine or back	17 (38)	24 (55)	20 (45)
Knee	18 (40)	9 (20)	14 (32)
Other	10 (22)	11 (25)	10 (23)
Duration of disease, mean (SE)	10 (1)	9 (2)	8 (1)

*CR indicates controlled release; q12h, every 12 hours.

†Categorical scale (0 indicates none; 1, slight; 2, moderate; and 3, severe); average of morning, noon, evening, and night assessments.

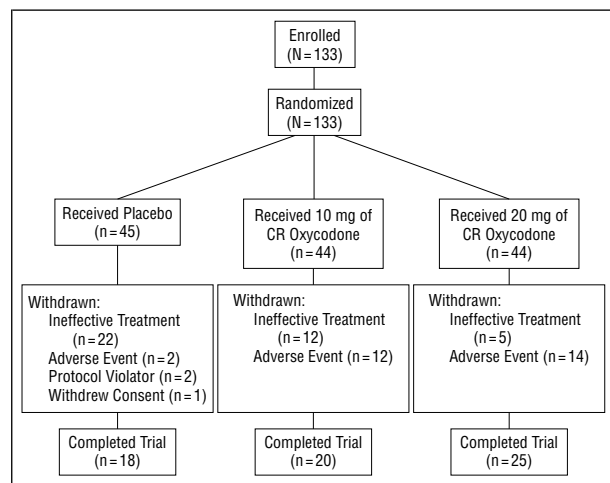


Figure 1. Disposition of patients enrolled in the double-blind, placebo-controlled trial of controlled-release (CR) oxycodone, 10 and 20 mg, every 12 hours.

CR oxycodone. Overall mean scores showed little difference in night, morning, afternoon, or evening pain assessments, demonstrating continuous stable pain control over 24 hours. The mean scores for each time of day differed by a maximum of 0.1 U in the placebo group and 0.2 U in the 2 CR oxycodone groups. There were no significant center \times treatment interactions. Baseline pain intensity was significant, but sex and age were not significant factors among the 3 treatment groups. At weeks 1 and 2, the Brief Pain Inventory assessments of pain intensity showed that use of 20 mg of CR oxycodone q12h was significantly more effective than placebo use ($P < .05$) in improvement from baseline for pain right now and for worst and average pain in the last 24 hours. At week 2, use of the 20-mg dose was significantly more effective than was use of placebo for least pain in the last 24 hours

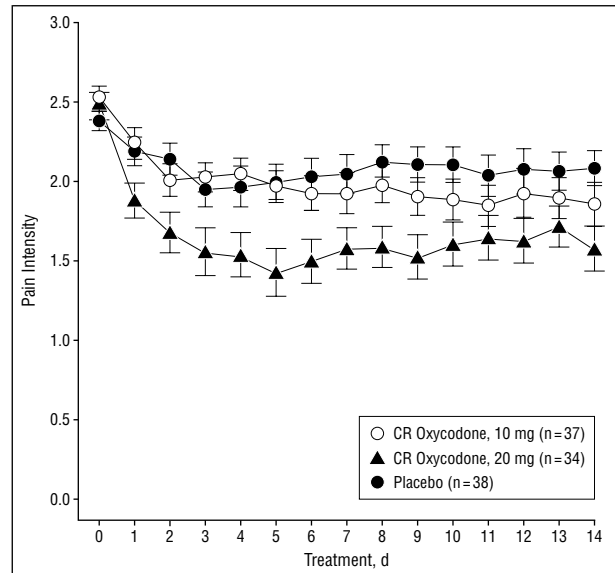


Figure 2. Daily mean pain intensity (0 indicates none; 1, slight; 2, moderate; and 3, severe) during 14-day double-blind treatment. CR indicates controlled release. Error bars represent SE.

and use of the 10-mg dose for worst and least pain in the last 24 hours.

The 20-mg CR oxycodone group showed significant ($P < .05$) mean improvements from baseline in mitigating the interference of pain on mood, sleep, and enjoyment of life (**Figure 3**). Interference of pain on walking ability, general activity, normal work, and relations with others showed some improvement from baseline but did not reach statistical significance. The 10-mg CR oxycodone group showed larger improvements from baseline than did the placebo group for pain and function, but differences were not statistically significant.

At baseline, activities and lifestyle questionnaire scores ranged from 1.1 (0.1) to 2.3 (0.1) on the 4-point scale. Thus, most patients were able to perform daily activities "without any difficulty" or "with some difficulty." Treatment with 10 or 20 mg of CR oxycodone q12h did not result in increased impairment in the performance of these functions and did not improve performance. Quality of sleep was significantly better in patients receiving 20 mg of CR oxycodone q12h than in those receiving placebo at week 1 and overall ($P < .05$).

Eighty-seven (65.4%) of 133 patients reported at least 1 treatment-related adverse experience during the study; the most common were known opioid-related side effects (**Table 2**). Common gastrointestinal events seemed to be dose related, whereas no dose relationship was apparent for CNS events. Using a logistic regression model, there were no significant differences in these adverse events between men and women. In patients 65 years and older vs those younger than 65 years, only somnolence was significantly more prevalent in elderly patients ($P = .02$). No adverse events were life threatening. There were no clinically significant safety observations concerning physical examination results, laboratory findings, or changes in vital signs.

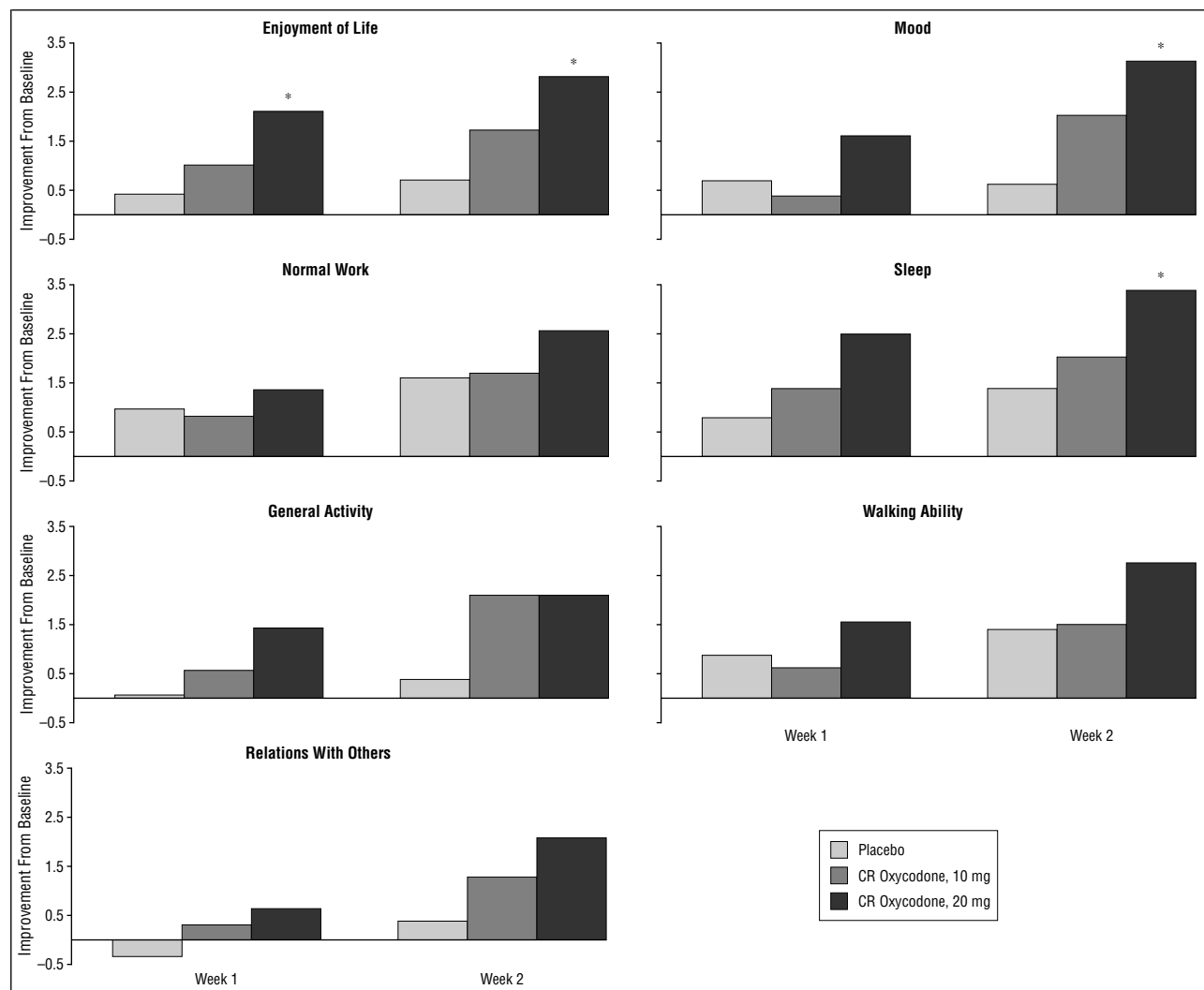


Figure 3. Mean improvement from baseline in mitigating interference of pain with lifestyle (using the Brief Pain Inventory and a numerical scale from 0-10). CR indicates controlled release. Asterisk indicates $P < .05$ better than placebo.

LONG-TERM EXTENSION TRIAL

Twenty-six men and 80 women aged 32 to 88 years (mean, 62 years) enrolled in the long-term trial. Forty-five patients (42.5%) were 65 years or older. Seventy-three patients (68.9%) continued NSAID therapy during the long-term trial. Sixty patients (56.6%) discontinued treatment with CR oxycodone for the following reasons: adverse events (32 patients), ineffective treatment (8 patients), intercurrent illness (6 patients), withdrew consent (5 patients), lost to follow-up (3 patients), noncompliance (3 patients), no longer required opioid therapy (2 patients), and physician's advice (1 patient). The most common adverse events leading to discontinuation were constipation, nausea, pruritus, somnolence, and nervousness. One of the 3 noncompliant patients took more drug than prescribed. Thirty-one patients were required to discontinue treatment with CR oxycodone because the sponsoring company ended the study. At that time, 58 patients had completed 6 months of treatment, 41 had completed approximately 12 months (48 weeks), and 15 had completed 18 months. Analgesics used after study

completion were recorded for 48 patients, 46 of whom continued opioid therapy.

The dose of CR oxycodone became constant at approximately 40 (2) mg/d by week 16, ranging from 39 (2) to 41 (4) mg/d between weeks 16 and 72 (**Figure 4**). The highest percentage of patients, 65.1% (69/106), required dose titration at week 2. The dose was increased in all but 7 of these patients, and 67 patients required asymmetrical titration. After week 8, when 35.2% of patients required titration, the percentage declined from 9.5% to 21.3% per visit for the remainder of the trial. A higher percentage of patients required downward titration as the trial progressed. Thirty-nine patients (36.8% of those enrolled) were receiving asymmetrical doses at the time of completion or discontinuation, with 32 receiving a higher dose in the morning than in the evening.

Pain was controlled below a "moderate" level throughout the long-term trial, with no statistically significant trends from week 2 to the end of the trial. Pain intensity was 1.7 (0.1) at 6 months and ranged from 1.7 (0.1) to 1.9 (0.1) during weeks 32 to 72 (Figure 4). At the end of each scheduled respite, pain intensity rose to

Table 2. Treatment-Related Adverse Experiences Reported by More Than 10% of 133 Patients During the Placebo-Controlled Trial*

Adverse Experience	Placebo Group (n = 45)	CR Oxycodone q12h Group	
		10 mg (n = 44)	20 mg (n = 44)
Nausea	5 (11)	12 (27)	18 (41)
Constipation	3 (7)	10 (23)	14 (32)
Somnolence	2 (4)	11 (25)	12 (27)
Vomiting	3 (7)	5 (11)	10 (23)
Dizziness	4 (9)	13 (30)	9 (20)
Pruritus	1 (2)	8 (18)	7 (16)
Headache	3 (7)	4 (9)	5 (11)

*Values are expressed as number (percentage) of patients. CR indicates controlled release; q12h, every 12 hours.

above moderate, with scores ranging from 2.3 (0.1) to 2.5 (0.2). These average scores were close to the mean score at baseline of the placebo-controlled trial (Table 1). More than 80% of patients rated their level of pain as unacceptable during each respite.

The activities and lifestyle questionnaire findings showed that patients were not highly impaired when they entered the long-term trial. They could perform activities of daily living "without any difficulty" or "with some difficulty." At 6 months and for the remainder of the trial, there were small changes of 0.1 to 0.4 U on the 4-point scale, indicating that CR oxycodone therapy did not lead to a deterioration or an improvement in function. Patients rated quality of sleep as "fair" when they entered the long-term trial (3.1 [0.1]) and fair to "good" at 6 months (3.6 [0.1]). This was constant for the remainder of the trial, with scores ranging from 3.4 (0.2) to 3.7 (0.1). The number of night awakenings due to pain was 1.6 (0.2) at baseline, 0.7 (0.1) at 6 months, and 0.6 (0.2) to 1.4 (0.3) for the remainder of the trial.

The adverse experiences reported by more than 10% of patients during the long-term trial were those usually anticipated with use of opioid analgesics: constipation (55 patients), somnolence (32 patients), nausea (25 patients), pruritus (21 patients), nervousness (16 patients), headache (14 patients), and insomnia (14 patients). The duration ratio (calculated as the number of days a patient experienced the adverse event divided by the number of days the patient was treated with CR oxycodone, expressed as a percentage) for 4 typical opioid side effects—nausea, pruritus, somnolence, and constipation—decreased during the trial. This downward trend was statistically significant for all 4 adverse events ($P < .001$) (**Figure 5**). Thirteen patients were hospitalized during the 18-month trial. In 8 of these patients, the investigator judged that the hospitalization was unrelated to CR oxycodone therapy. Five patients were hospitalized for adverse events in which a causal relationship to CR oxycodone use could not be ruled out, all of which resolved with treatment: 2 for abdominal pain, 1 for constipation, 1 for withdrawal symptoms, and 1 for a fall secondary to confusion and disorientation. The last patient was receiving many CNS-active medications. The

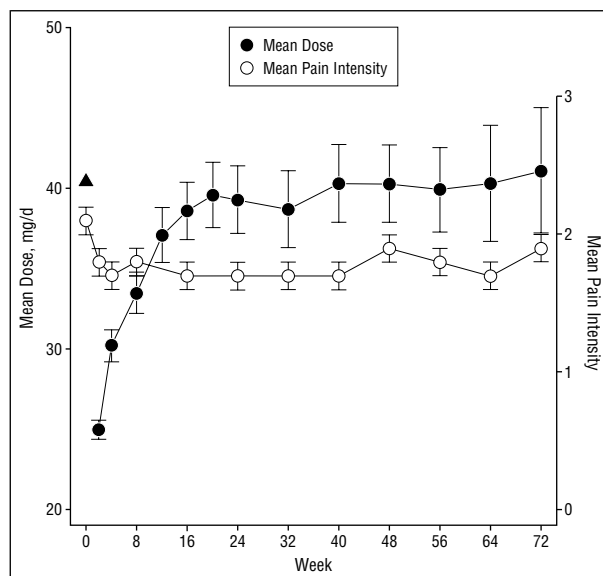


Figure 4. Daily dose of controlled-release oxycodone administered and pain intensity (0 indicates none; 1, slight; 2, moderate; and 3, severe) during the long-term trial. The black triangle indicates the baseline pain intensity lead-in. Error bars represent SE.

confusion and disorientation were attributed to doubling the dose of one of these medications (flurazepam hydrochloride) in the presence of other CNS-active medications, including CR oxycodone. The patient who was hospitalized with withdrawal symptoms had completed the study on the previous day and had been receiving CR oxycodone, 70 mg/d; symptoms resolved after 3 days. A second patient, who was receiving 60-mg/d CR oxycodone, experienced withdrawal symptoms after running out of study medication. The patient had not reported withdrawal symptoms during scheduled respites from doses of 30 or 40 mg/d. Withdrawal syndrome was not reported as an adverse event for any patient during scheduled respites. Adverse experiences reported by more than 10% of patients during the scheduled respites were nervousness (9 patients) and insomnia (8 patients). During the long-term trial, there were no clinically significant safety observations concerning physical examination results, laboratory findings, or changes in vital signs.

COMMENT

Moderate to severe osteoarthritis pain is difficult to manage adequately with non-centrally acting analgesics. Acetaminophen and NSAIDs have an analgesic ceiling⁷ and potential toxic effects at high doses.^{8,9} Toxic effects associated with long-term use of high-dose NSAIDs are of particular concern in elderly patients,^{9,10} the population most likely to experience osteoarthritis. As the population ages, the demand for effective analgesics for treatment of osteoarthritis pain is likely to increase. Opioid analgesic therapy might offer an alternative for patients whose pain cannot be controlled by use of weaker analgesics or in whom use of NSAIDs is contraindicated.³³ Although the benefits of long-term use of opioids for chronic noncancer pain is debated in the literature,¹⁴⁻¹⁹ there is growing recognition that some patients

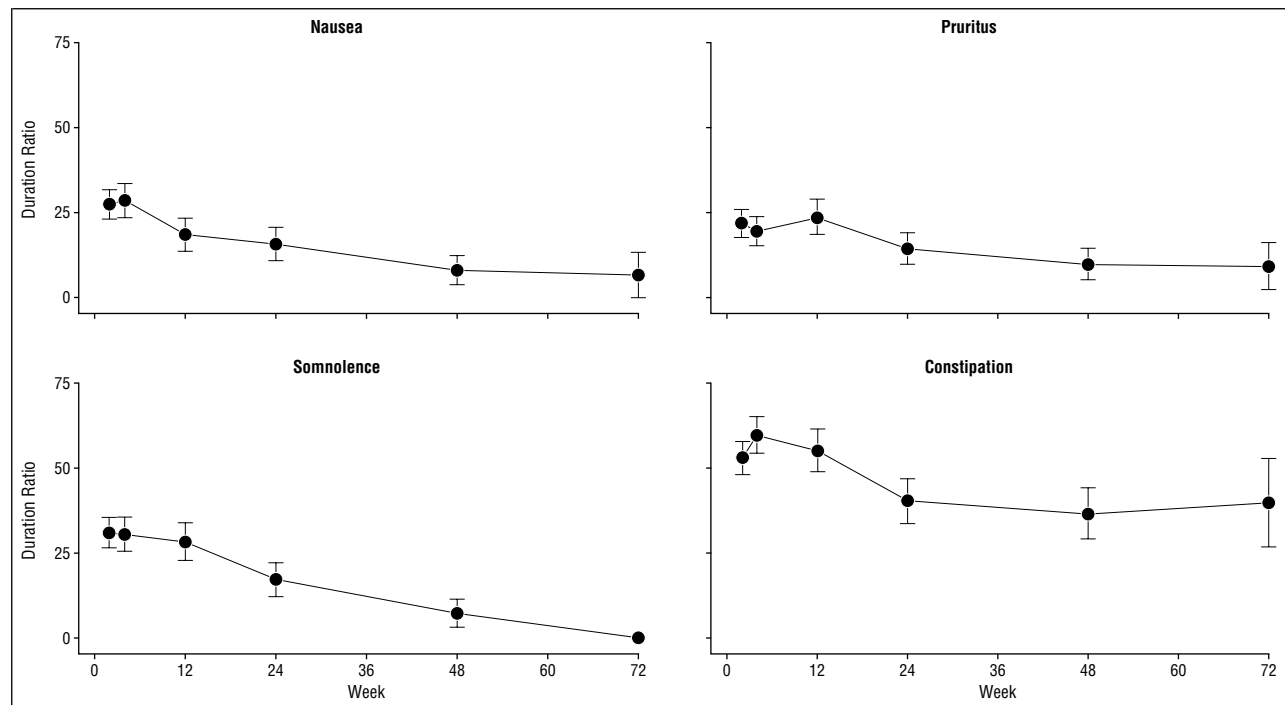


Figure 5. Mean duration ratio (calculated as the number of days the patient experienced the adverse event divided by number of days the patient was treated with controlled-release oxycodone, expressed as a percentage) of 4 opioid side effects during the long-term trial. Error bars represent SE.

achieve pain relief without deterioration in function when opioids are included as part of a comprehensive pain management program.²⁰⁻²⁵

Results of our clinical trials showed that CR oxycodone therapy provided clinically meaningful, sustained analgesia with a typical opioid side effect profile during short- and long-term treatment of moderate to severe osteoarthritis pain. Use of CR oxycodone at a dose of 20 mg q12h provided a clinically meaningful reduction in pain within 24 hours and was significantly more effective than placebo during the 2-week study. Improved analgesia was accompanied by significant reductions in the interference of pain with mood, sleep, and enjoyment of life and by significant improvement in quality of sleep. During long-term therapy, the mean dose of CR oxycodone stabilized at approximately 40 mg/d after an initial titration period, while analgesia was maintained throughout the trial. Scheduled respites supported the continuing need for opioid analgesia in these patients, with pain intensity returning to prestudy baseline levels when CR oxycodone therapy was discontinued. Patients' ability to conduct their daily activities was neither impaired nor improved during short- or long-term therapy with CR oxycodone. Our study population exhibited little functional impairment at baseline, leaving little room for treatment-related improvement.

Overall discontinuation rates were similar in the double-blind (52.6%) and long-term (56.6%) trials. The rate of discontinuation for ineffective treatment was related to the CR oxycodone dose; rates were similarly low in patients treated with 20 mg of CR oxycodone q12h in the placebo-controlled trial and in patients whose dose was individually titrated in the long-term trial (to an average dose of 40 mg/d). In contrast, discontinuation rates

for adverse events were similar across CR oxycodone groups, whether the dose was fixed or titrated and despite the differences in duration of therapy in the 2 trials. In a trial³⁴ of CR oxycodone therapy in cancer pain, discontinuations for ineffective treatment were lower when the dose was titrated compared with a fixed dose based on previous opioid use, whereas discontinuations for adverse events were similar whether the dose was titrated or fixed. Individual dose titration and careful patient monitoring, along with appropriate treatment of opioid-related side effects, are important components of the pain management program when opioids are used.³³

During short- and long-term treatment with CR oxycodone, the most commonly reported adverse experiences were characteristic of opioid use. The duration of nausea, pruritus, and somnolence relative to CR oxycodone exposure decreased during the trial. Decreasing frequency of nausea and sedation has been reported¹¹ during long-term opioid therapy for cancer pain. The present study also showed a decreasing duration of constipation relative to CR oxycodone exposure, which likely reflects effective preventive therapy because experience in cancer pain indicates that constipation generally persists during long-term opioid therapy.¹¹ There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites, indicating that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient's condition so warrants.

Results of our studies in patients with moderate to severe osteoarthritis pain support those of previous controlled trials^{26,27} demonstrating the analgesic efficacy of CR opioids for treating chronic noncancer pain and pre-

vious clinical experience²⁰⁻²⁵ demonstrating that some patients with noncancer pain benefit from the pain relief offered by opioids without a deterioration in function. Management of chronic osteoarthritis pain requires non-pharmacological and pharmacological approaches. When use of weaker analgesics is ineffective or contraindicated, use of opioid analgesics can be of benefit when they are incorporated into a multidisciplinary, individualized treatment program. Key components of such a program include patient screening, regular pain assessments, dose titration to an acceptable balance between analgesia and side effects, dosing scheduled by the clock, control of breakthrough pain, and ongoing management of side effects.³³ Within such a framework, patients with osteoarthritis can benefit from the analgesic effects of opioids and minimize their adverse effects.

In conclusion, around-the-clock CR oxycodone therapy seemed to be an effective and safe treatment modality for patients with chronic, moderate to severe pain associated with osteoarthritis. Effective analgesia was accompanied by a reduction in the interference of pain with mood, sleep, and enjoyment of life. Analgesia was maintained during long-term treatment, and the daily CR oxycodone dose remained stable after an initial titration period. Common opioid-related side effects were reported during CR oxycodone therapy, several of which decreased in duration as therapy continued. Patients' ability to function was not compromised during short- and long-term treatment with CR oxycodone.

Accepted for publication July 19, 1999.

This study was sponsored by Purdue Pharma LP, Norwalk, Conn.

Presented in part at the 97th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Lake Buena Vista, Fla, March 20, 1996; and at the 8th World Congress on Pain, International Association for the Study of Pain, Vancouver, British Columbia, August 18, 1996.

Reprints: Sanford H. Roth, MD, ArthroCare, 3330 N Second St, Suite 601, Phoenix, AZ 85012.

REFERENCES

- Cooper C. Occupational activity and the risk of osteoarthritis. *J Rheumatol*. 1995; 22(suppl 43):10-12.
- Katz WA. Pharmacology and clinical experience with tramadol in osteoarthritis. *Drugs*. 1996;52(suppl 3):39-47.
- Hicks JE, Gerber LH. Rehabilitation in the management of patients with osteoarthritis. In: Moskowitz RW, Howell DS, Goldberg VM, Mankin HJ, eds. *Osteoarthritis: Diagnosis and Medical/Surgical Management*. 2nd ed. Philadelphia, Pa: WB Saunders Co; 1992:427-464.
- Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis, part I: osteoarthritis of the hip. *Arthritis Rheum*. 1995; 38:1535-1540.
- Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis, part II: osteoarthritis of the knee. *Arthritis Rheum*. 1995; 38:1541-1546.
- Wollheim FA. Current pharmacological treatment of osteoarthritis. *Drugs*. 1996; 52(suppl 3):27-38.
- Beaver WT. Impact of non-narcotic oral analgesics on pain management. *Am J Med*. 1988;84(suppl 5A):3-15.
- Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1994;331:1675-1679.
- Kirchner JT. Nonsteroidal anti-inflammatory drug use in the elderly: issues of compliance and safety. *J Am Osteopath Assoc*. 1994;94:300-304.
- Roth SH. NSAID gastropathy: a new understanding. *Arch Intern Med*. 1996;156: 1623-1628.
- Jacox A, Carr DB, Payne R, et al. *Clinical Practice Guideline Number 9: Management of Cancer Pain*. Rockville, Md: Agency for Health Care Policy and Research, US Dept of Health and Human Services; 1994:39-74. AHCPR publication 94-0592.
- American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. 3rd ed. Skokie, Ill: American Pain Society; 1992.
- Cancer Pain Relief With a Guide to Opioid Availability*. 2nd ed. Geneva, Switzerland: World Health Organization; 1996.
- Finlayson RE, Maruta T, Morse RM, Swenson WM, Martin MA. Substance dependence and chronic pain: profile of 50 patients treated in an alcohol and drug dependence unit. *Pain*. 1986;26:167-174.
- Finlayson RE, Maruta T, Morse RM, Martin MA. Substance dependence and chronic pain: experience with treatment and follow-up results. *Pain*. 1986;26:175-180.
- Maruta T, Swanson DW. Problems with the use of oxycodone compound in patients with chronic pain. *Pain*. 1981;11:389-396.
- Maruta T, Swanson DW, Finlayson RE. Drug abuse and dependency in patients with chronic pain. *Mayo Clin Proc*. 1979;54:241-244.
- McNairy SL, Maruta T, Ivnik RJ, Swanson DW, Ilstrup DM. Prescription medication dependence and neuropsychologic function. *Pain*. 1984;18:169-177.
- Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. *J Pain Symptom Manage*. 1993;8:279-288.
- Taub A. Opioid analgesics in the treatment of chronic intractable pain of non-neoplastic origin. In: Kitahata LM, Collins JG, eds. *Narcotic Analgesics in Anesthesiology*. Baltimore, Md: Williams & Wilkins; 1982:199-208.
- Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25:171-186.
- Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. *J Pain Symptom Manage*. 1992;7:69-77.
- France RD, Urban BJ, Keefe FJ. Long-term use of narcotic analgesics in chronic pain. *Soc Sci Med*. 1984;19:1379-1382.
- Tennant FS Jr, Robinson D, Sagharian A, Seecof R. Chronic opioid treatment of intractable nonmalignant pain. *Pain Manage*. January/February 1988:18-26.
- Urban BJ, France RD, Steinberger EK, Scott DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb pain. *Pain*. 1986;24:191-196.
- Arkininstall W, Sandler A, Goughnour B, Babul N, Harsanyi Z, Darke AC. Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized, placebo-controlled clinical trial. *Pain*. 1995;62:169-178.
- Moulin DE, Iezzi A, Amireh R, Sharpe WKJ, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet*. 1996;347:143-147.
- Max MB, Laska EM. Single-dose analgesic comparisons. In: Max M, Portenoy R, Laska E, eds. *Advances in Pain Research and Therapy*. Vol 18. New York, NY: Raven Press; 1991:55-95.
- Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, eds. *Handbook of Pain Assessment*. New York, NY: Guilford Press; 1992:135-151.
- Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*. 1983;17:197-210.
- Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? grading pain severity by its interference with function. *Pain*. 1995;61:277-284.
- Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum*. 1983;26:1346-1353.
- Roth SH, Reder RF. The role of opioids in the treatment of osteoarthritis. *Resident Staff Physician*. 1998;44:31-36.
- Kaplan R, Parris WC-V, Citron ML, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *J Clin Oncol*. 1998;16:3230-3237.